NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Secukinumab for treating non-radiographic axial spondyloarthritis [ID1419]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Secukinumab for treating non-radiographic axial spondyloarthritis

Contents:

The following documents are made available to consultees and commentators:

The **final scope** **and** **final stakeholder list** are available on the NICE website.

1. **Company submission** from **Novartis**

2. **Clarification questions (part 1 & part 2) and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. British Society for Rheumatology
   b. National Axial Spondyloarthritis Society (NASS)

4. **Expert personal perspectives** from:
   a. Dr Raj Sengupta, Consultant Rheumatologist – clinical expert, nominated by Novartis Pharmaceuticals UK Ltd.
   b. Dr Louise Warburton, Associate Medical Director – clinical expert, nominated by the Primary Care Rheumatology and MSK Medicine Society

5. **Evidence Review Group report prepared by Centre for Reviews and Dissemination and Centre for Health Economics Technology Assessment Group, University of York**

6. **Evidence Review Group – factual accuracy check**

7. **Technical Report**

8. **Technical engagement response** from **Novartis**

9. **Technical engagement response from consultees and commentators:**
   a. British Society for Rheumatology

10. **Evidence Review Group critique of company response to technical engagement** prepared by Centre for Reviews and Dissemination and Centre for Health Economics Technology Assessment Group, University of York

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Secukinumab for treating non-radiographic axial spondyloarthritis [ID1419]

Document B

Company evidence submission

December 2019

File name	Version	Contains confidential information	Date
ID1419_Secukinumab_nr-AxSpA_Form B_FINAL	**FINAL**	**Yes**	**10th Dec 2019**

Contents

Tables and figures

List of abbreviations

AE	Adverse event
AIC	Akaike information criterion
ANCOVA	Analysis of covariance
AS	Ankylosing spondylitis
ASAS	Assessment of Spondylarthritis International Society
ASQoL	Ankylosing Spondylitis Quality of Life
axSpA	Axial spondylarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BIC	Bayesian information criterion
BMI	Body mass index
BNF	British National Formulary
CC	Conventional care
CEAC	Cost-effectiveness acceptability curve
CEP	Cost-effectiveness plane
CI	Confidence interval
CrI	Credible interval
CRP	C-reactive protein
DIC	Deviance Information Criterion
DMARD	Disease-modifying anti-rheumatic drug
EAIR	Exposure-adjusted incidence rate
EMA	European Medicines Agency
ERAP	Endoplasmic reticulum aminopeptidase
ERG	Evidence review group
ESR	Erythrocyte sedimentation rate
EQ-5D	EuroQol 5 dimensions
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
FDA	US Food and Drug Administration
GP	General practitioner
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
hsCRP	High sensitivity C-reactive protein
IBD	Inflammatory bowel disease
ICER	Incremental cost-effectiveness ratio
IL	Interleukin
IRT	Interactive response technology

LS	Least squares
MAR	Missing at random
MCS	Mental component summary
MD	Mean Difference
MHC	Major histocompatibility complex
MI	Multiple imputation
MMRM	Mixed-effects model repeated measures
MRI	Magnetic resonance imaging
mSASSS	Modified Stoke Ankylosing Spondylitis Spinal Score
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMSC	Non-melanoma skin cancer
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PCS	Physical component summary
PFS	Pre-filled syringe
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PY	Patient years
Q4W	Every four weeks
QALY	Quality-adjusted life year
r-axSpA	Radiographic axial spondyloarthritis
RCT	Randomised controlled trial
RR	Relative risk
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SF-36	Short Form 36-Item Survey
SI	Sacroiliac
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard-of-care
SOC	System organ class
TNFα	Tumour necrosis factor alpha
TNF-IR	Tumour necrosis factor inadequate response
VAS	Visual analogue scale
WPAI-GH	Work Productivity and Activity Impairment Questionnaire – General Health

Executive summary

Non-radiographic axial spondyloarthritis

- Non-radiographic axial spondyloarthritis (nr-axSpA) is a chronic inflammatory disease that, together with ankylosing spondylitis (AS; also known as axial spondyloarthritis [axSpA] with radiographic damage) is part of the axSpA disease spectrum
- Key symptoms include chronic back pain and stiffness predominantly of the pelvis and lower back, with gradual onset over weeks and months, and persisting for more than 3 months. Patients experience early-morning stiffness and pain and can be awakened by pain in the second part of the night
- For patients who have not responded to, or who cannot tolerate, non-steroidal anti-inflammatory drugs (NSAIDs), tumour necrosis factor alpha (TNFα) inhibitors are currently the only class of drugs recommended by the National institute for Health and Care Excellence (NICE) for treatment of the condition
- However, there remains a significant unmet need for new treatment options with new mechanisms of action, as TNFα inhibitors are associated with efficacy, safety and health-related quality of life limitations

Secukinumab (Cosentyx®)

- Secukinumab is a monoclonal antibody that binds to and neutralises the activity of the proinflammatory cytokine, interleukin-17A (IL-17A), a key cytokine in the pathogenesis of spondyloarthritis
- Secukinumab is anticipated to be licensed for the treatment of active nr-axSpA with objective signs of inflammation as indicated by elevated c-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to NSAIDs

Clinical effectiveness of secukinumab

- The PREVENT randomised controlled trial (RCT) of 555 patients with active nr-axSpA demonstrated that secukinumab 150 mg was associated with improved clinical outcomes vs placebo

- At 16 weeks, TNFα-naïve patients with nr-axSpA treated with secukinumab 150 mg Load[a] and secukinumab 150 mg No Load achieved a statistically significantly better Assessment of Spondylarthritis International Society 40 (ASAS40) response than placebo
  - secukinumab 150 mg Load (41.5%) vs placebo (29.2%), p=0.0197
  - secukinumab 150 mg No Load (42.2%) vs placebo (29.2%), [redacted]
- At 16 weeks, the full cohort of patients (TNFα-naïve and TNFα-experienced) with nr-axSpA treated with secukinumab 150 mg Load and secukinumab 150 mg No Load achieved a statistically significantly better ASAS40 response than placebo
  - secukinumab 150 mg Load (40.0%) vs placebo (28.0%), [redacted]
  - secukinumab 150 mg No Load (40.8%) vs placebo (28.0%), [redacted]
- Statistically significantly better results compared with placebo were also achieved by patients with nr-axSpA treated with secukinumab 150 mg Load and secukinumab 150 mg No Load for outcomes of [redacted] Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) change from baseline, BASDAI50 response, high-sensitivity c-reactive protein (hsCRP) change from baseline, Bath Ankylosing Spondylitis Functional Index (BASFI) change from baseline, MRI sacroiliac (SI) joint oedema score change from baseline, [redacted] short-form-36 (SF-36) physical component summary (PCS) [redacted]) change from baseline, Ankylosing Spondylitis Quality of Life (ASQoL) change from baseline, and ASAS partial remission

- In the PREVENT trial, treatment with secukinumab 150 mg (with or without loading) was well tolerated, and no new or unexpected safety signals were identified
  - Most adverse events (AEs) reported were mild or moderate in severity for all treatment groups, and severe AEs were of low frequency in all groups over the entire treatment period

[a] Secukinumab 150 mg Load included dosing with secukinumab 150 mg at baseline, Weeks 1, 2 and 3, and every 4 weeks starting at Week 4; Secukinumab 150 mg No Load included dosing with secukinumab 150 mg at baseline and with placebo at Weeks 1, 2 and 3, followed by secukinumab 150 mg every 4 weeks starting at Week 4.

[redacted]

Cost-effectiveness of secukinumab

- The economic evaluation compared secukinumab with all approved TNFα inhibitors in nr-axSpA and conventional care (CC) in the biologic-naïve population (primary analysis), and compared secukinumab against CC in the biologic-experienced population (secondary analysis)
- The results of the primary analysis (biologic-naïve patients) showed secukinumab to be the biologic associated with the lowest overall costs
- Only adalimumab biosimilar was associated with a lower incremental cost-effectiveness ratio (ICER) vs CC than secukinumab; however, the results were similar (£5,445 and £7,459 per quality-adjusted life year [QALY] gained, respectively)
- In the secondary analysis (biologic-experienced patients), secukinumab was shown to be dominant compared with CC, with [redacted]
- Recommendations issued by NICE in TA383 and TA497 included statements that if more than one treatment is considered suitable, the least expensive should be chosen; adopting similar wording for guidance on secukinumab would ensure that the best value biologic is used in clinical practice

Added value of secukinumab

- [redacted]

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Secukinumab (Cosentyx®) is currently indicated for the treatment of active ankylosing spondylitis (also known as axSpA with radiographic damage) in adults who have responded inadequately to conventional therapy.

This submission covers the technology's anticipated marketing authorisation extension: secukinumab (Cosentyx®) is anticipated to be licensed for the treatment of active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated c-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs).

The decision problem addressed by this submission is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with nr-axSpA with objective signs of inflammation, whose disease has responded inadequately to, or who are intolerant to, NSAIDs	As per scope	–
Intervention	Secukinumab	As per scope	–
Comparator(s)	• Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Established clinical management without biological treatments	As per scope	–
Outcomes	The outcome measures to be considered include: • disease activity • functional capacity • disease progression • pain • peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • Symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • adverse effects of treatment • health-related quality of life	As per scope, except for peripheral arthritis, dactylitis, and symptoms of extra-articular manifestations.	These are not measured outcomes within the secukinumab Phase III study (PREVENT, NCT02696031).
Subgroups to be considered	If the evidence allows the subgroups of people who have had or not had prior exposure to biological therapy.	As per scope†	–

†Note that in PREVENT, only 54 patients (9.7%) had previously received a prior TNFα inhibitor, so this subgroup analysis is based on a small sample of patients.
Abbreviations: nr-axSpA, non-radiographic axial spondyloarthritis; NSAIDs, non-steroidal anti-inflammatory drugs.

B.1.2 Description of the technology being appraised

In Appendix C include the summary of product characteristics or information for use, and the European public assessment report, scientific discussion or drafts.

Table 2: Technology being appraised

UK approved name and brand name	Secukinumab (Cosentyx®)
Mechanism of action	Secukinumab is a high-affinity, recombinant, fully human monoclonal antibody that binds to and neutralises the activity of the proinflammatory cytokine IL-17A. By inhibiting the interaction of IL-17A with its receptor, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage, and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases, including nr-axSpA and AS.
Marketing authorisation/CE mark status	A regulatory submission was made to the EMA on 28/08/2019. CHMP positive opinion is expected in March 2020 with marketing authorisation expected to be granted by the European Commission by May 2020.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Secukinumab (Cosentyx®) is currently indicated for the treatment of active ankylosing spondylitis (also known as axSpA with radiographic damage) in adults who have responded inadequately to conventional therapy. It is also indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy, and for the treatment of active psoriatic arthritis (alone or in combination with methotrexate [MTX]) in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate The anticipated indication update is for axial spondyloarthritis (axSpA) ***with or without*** radiographic damage: • Ankylosing spondylitis (AS) / axSpA with radiographic damage. Cosentyx is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. • Non-radiographic axial spondyloarthritis (nr-axSpA) / axSpA without radiographic damage. Cosentyx is indicated for the treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs).
Method of administration and dosage	Subcutaneous (SC) injection with a SensoReady Autoinjector pen or pre-filled syringe. The recommended dose is 150 mg administered subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. After proper training in subcutaneous injection technique, patients may self-inject if a physician determines that this is appropriate. However, the physician should ensure appropriate follow-up of patients.
Additional tests or investigations	No additional tests or investigations are needed compared with current clinical practice.

List price and average cost of a course of treatment	Acquisition cost (for 2 x 150 mg)
	• List price: £1,218.78
	• PAS price: [redacted]
	Annual cost of treatment
	• List price:
	  ○ First year: £9,750.24
	  ○ Subsequent years: £7,312.68
	• PAS price:
	  ○ First year: [redacted]
	  ○ Subsequent years: [redacted]

Patient access scheme (if applicable)	A patient access scheme (PAS) has been agreed with the Department of Health. This scheme provides a variable rate discount on the NHS List Price to maintain a fixed purchase price. This is applied as a simple discount to the list price of secukinumab, with the discount applied at the point of purchase or invoice.

B.1.3 Health condition and position of the technology in the treatment pathway

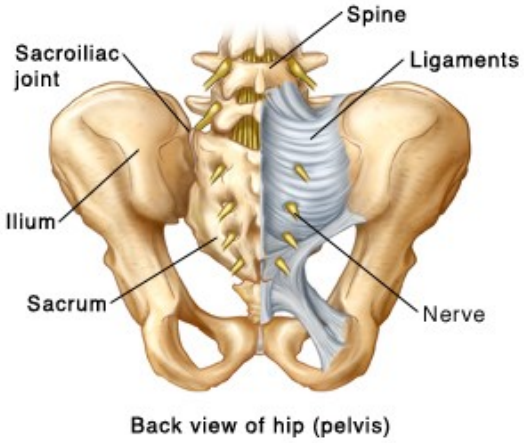
- Non-radiographic axial spondyloarthritis (nr-axSpA) is a chronic inflammatory disease that is part of the axSpA disease spectrum – the burden of disease is comparable between patients with nr-axSpA and those with ankylosing spondylitis (AS)
- Common symptoms include chronic back pain, stiffness, fatigue, poor sleep quality and night-time waking, but the condition can also cause peripheral and extra-articular symptoms including arthritis, dactylitis, uveitis and psoriasis
- The onset of symptoms in the second to third decade of life has a considerable impact on a personal level, in terms of careers and relationships, and on an economic level, through lost productivity
- Current NICE guidance recommends tumour necrosis factor alpha (TNFα) inhibitors for treating severe nr-axSpA in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs (NSAIDs)
- However, a large proportion of patients do not respond to TNFα inhibitors, which can lead to high discontinuation rates and treatment switching, and there is a small but significant risk of serious opportunistic infections due to their immunosuppressive properties
- There remains a significant unmet need in nr-axSpA; secukinumab offers patients a new treatment option with a novel mechanism of action

B.1.3.1 Overview

nr-axSpA (also known as axSpA without radiographic damage) is a chronic inflammatory disease that, together with AS, is part of the axSpA disease spectrum. The condition predominantly affects the spine and sacroiliac joints connecting the sacrum and ilium bones of the pelvis (Figure 1) causing chronic lower back pain and stiffness. Other body areas can also be affected (Figure 2) resulting in symptoms including peripheral arthritis, enthesitis (inflammation at the site where ligaments or

tendons attach to the bone), uveitis (inflammation of the middle layer of the eye), psoriasis and inflammatory bowel disease (IBD).

Figure 1: Anatomy of the sacroiliac joints



Source: https://www.fairview.org/patient-education/40548

nr-axSpA is distinguished from AS by the absence of visible structural damage in the sacroiliac joints or spine using plain radiography (1, 2), but the burden of disease and effect on quality of life are similar between nr-axSpA and AS (3-5). Furthermore, over a quarter of patients (27%) are diagnosed with axial spondyloarthritis rather than either AS or nr-axSpA (6), and the ICD-11 disease classification system does not distinguish between the two (7).

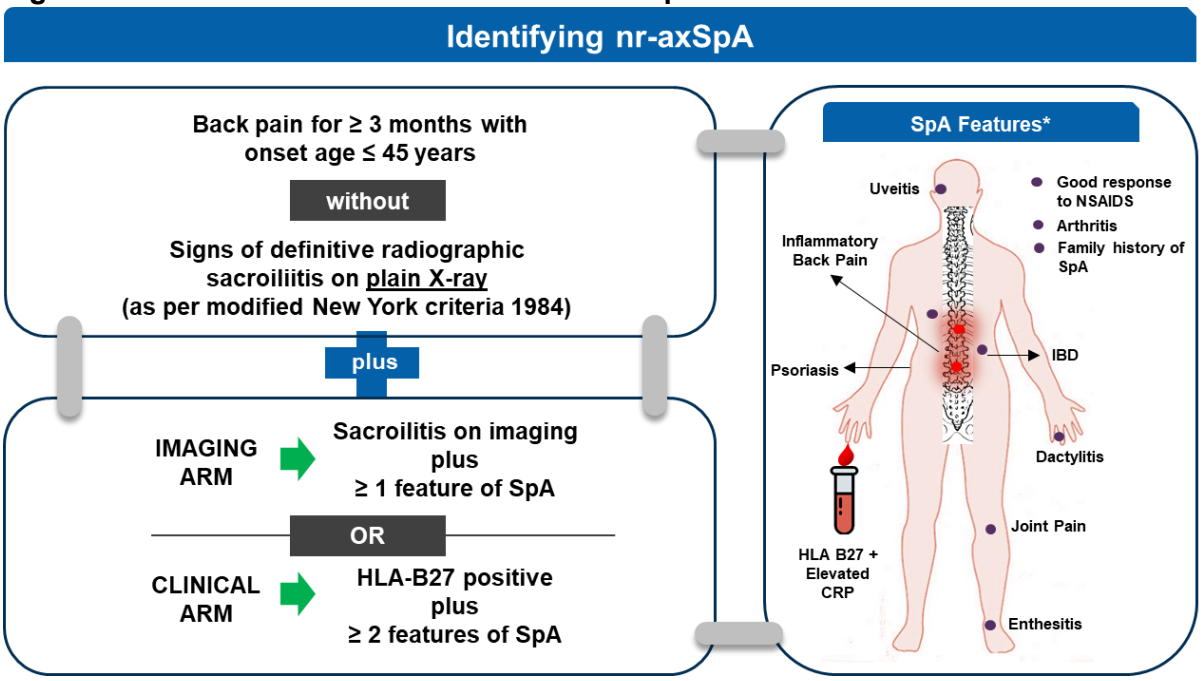
The significant pain (i.e. nocturnal pain), poor sleep quality, morning stiffness, impaired mobility and impairment of function experienced by patients reduces health-related quality of life (3), increases health service costs (8), and reduces work productivity (9). This is particularly important given that the disease usually starts in the third decade of life, with the average age at diagnosis being 24 years (10).

B.1.3.2 Classification criteria

The 2009 ASAS criteria (11) (Figure 2) have been widely adopted by the international rheumatology community (12). Prior to the development of these criteria, no standardised method existed for classifying nr-axSpA. As radiographic changes in the sacroiliac joints can take several years to manifest, the modified New York criteria used to classify AS are considered inadequate, as they can only be fulfilled if radiographic changes are evident (13).

Using ASAS 2009 criteria, patients are classified as having nr-axSpA if they have had back pain for at least three months, with onset before the age of 45 years, without signs of definitive sacroiliitis on plain X-ray. They must also fulfil criteria from the clinical or imaging (by magnetic resonance imaging [MRI]) arms of the classification (Figure 2).

Figure 2: ASAS classification criteria for nr-axSpA



Abbreviations: ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; CRP, C-reactive protein; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis.

B.1.3.3 Epidemiology

Prevalence data are sparse due to disease heterogeneity, slow progression and delay in diagnosis. Reported prevalence estimates range from around 0.1–0.4% in the general population (3, 14, 15), with NICE estimating that while approximately 200,000 people in the UK (0.3% of the population) are estimated to be affected by axSpA (10), only 71,000 of these have been diagnosed with the disease (16). As a whole, axSpA affects approximately equal proportions of males and females, however patients with nr-axSpA are more frequently female (2, 3).

Risk increases significantly in individuals with the human leukocyte antigen-B27 (HLA-B27) gene (Section B.1.3.4). Children of individuals with AS are twice as likely to develop the condition if they have inherited the HLA-B27 gene (10), and data from populations with AS indicates that prevalence mirrors the prevalence of HLA-B27.

Although only 8% of healthy white Europeans have this gene, up to 85% of people with AS have it – and those with the gene usually develop disease approximately 5 years earlier than those without the gene (2).

An increase in mortality has been reported in patients with axSpA, with cardiovascular disease consistently found as the leading cause of mortality in these patients (17). The condition is also associated with an increased risk of other potentially life-threatening problems, including osteoporosis and chest infections (10, 17, 18).

B.1.3.4 Natural history

Susceptibility is largely genetically determined (19). Most studies on the genetic basis of the disease have focused on AS populations rather than nr-axSpA populations or axSpA as a whole (2), but the findings are generalisable as both nr-axSpA and AS fall within the axSpA spectrum, and the burden disease is comparable between nr-axSpA and AS.

One large study found that approximately 20% of genetic predisposition was attributable to major histocompatibility complex (MHC) genes (mainly HLA-B27), and 7% to non-MHC genes (20). MHC genes encode proteins essential for the immune system to recognise foreign molecules, such as components of bacteria and viruses.

Additional genetic loci that may be important in axSpA susceptibility are endoplasmic reticulum aminopeptidase (ERAP; which is involved in presenting antigens to immune effector cells) and the interleukin-23 (IL-23) receptor (which activates T-helper cells which secrete IL-17 [the target of secukinumab], amongst others) (21).

The disease has a variable time-course, with symptoms fluctuating over many years – periods of reduced symptoms can be interrupted by flares, in which disease activity intensifies (10). The pace of progression varies widely between individuals, and follows a stop-start course with phases of slow or rapid progression (22). Approximately 10–40% of patients progress to AS over 2–10 years, and there is some evidence suggesting that not all patients experience progression (23).

In a study comparing the rates of progression in nr-axSpA patients meeting the two diagnostic arms of the ASAS 2009 criteria, subjects in the imaging arm were

3.5 times more likely to progress to AS than those in the clinical arm (20). Elevated baseline CRP (a marker of inflammation which circulates in the blood) is also a strong predictor of radiographic progression (odds ratio [OR] 3.65; $p<0.05$) (24).

Additional factors that are associated with an increased risk of progression to AS include active or chronic inflammatory changes in MRI of sacroiliac joints (sacroiliitis), high erythrocyte sedimentation rate (ESR), the presence of buttock pain, and HLA-B27 positivity, although evidence for an association between the latter and progression to AS is more mixed (23).

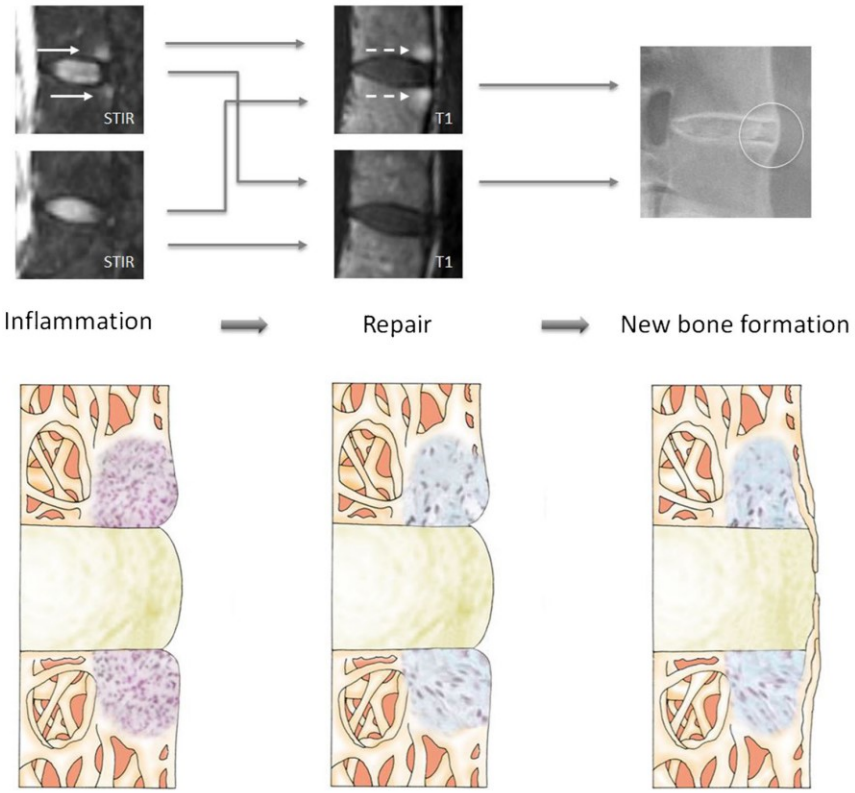
Patients with AS may eventually progress to become severely disabled due to fusion of bones in the spine and damage to other joints, such as the hips or knees (18).

Ubiquitous environmental triggers (such as infection) are suspected to initiate the disease process, although little is known about the nature of these triggers (10). The disease process in axSpA is outlined below (2, 10); the third step only occurs in patients with AS:

1. Inflammation occurs at the interface between cartilage and bone in the spine, sacroiliac joints (sacroiliitis), and entheses (enthesitis; entheses are the connective tissue between bone and tendons or ligaments). This inflammation may be initiated and maintained by mechanical stress, explaining why the disease affects load-bearing parts of the skeleton (25).
2. This leads to wearing of the bone at sites where ligaments or tendons attach (enthesopathy).
3. (In AS only) Inflammation reduces and the healing process begins, causing new bone (syndesmophytes) to develop in place of ligaments or tendons. When syndesmophytes develop movement becomes restricted. Repetition of the above process leads to further bone development and can result in fusion of the individual bones of the backbone.

Figure 3 illustrates the proposed sequence of inflammation, repair and new bone formation in axSpA. The final stage of this sequence represents AS patients.

Figure 3: Imaging the progression of axSpA



Source: Poddubnyy et al (2017) (26)
Abbreviations: axSpA, axial spondyloarthritis; MRI, magnetic resonance imaging.

IL-17A (the target of secukinumab) is a key cytokine in the pathogenesis of spondyloarthritis, driving inflammation, enthesitis and structural damage (27). Its pivotal role is best highlighted by the significant clinical efficacy shown with inhibitors of IL-17A in treating axSpA (28). IL-17A also participates in bone metabolism, and high numbers of IL-17+-producing cells have been observed at the primary inflammation site of affected facet joints in AS patients (29).

B.1.3.5 Symptoms

Key symptoms include chronic back pain and stiffness predominantly of the pelvis and lower back, with a gradual onset over weeks and months, and which persists for more than three months. Patients experience early-morning stiffness and pain, which improves with exercise but not with rest (10), and can be awakened by pain in the second part of the night (2). These characteristic features can be used to distinguish back pain associated with nr-axSpA from back pain due to other causes. Other common symptoms are fatigue, weight loss, feeling feverish and night sweats (10).

Some patients experience peripheral symptoms (in joints other than the spine or sacroiliac joints), the most common of which (observed in 30–50% of axSpA patients) are arthritis and enthesitis, which predominantly occur in the lower limbs and in an asymmetrical fashion. The joints are generally swollen and painful. Any entheseal site can be affected, but most commonly affected is the heel bone, where the plantar fascia ligament and Achilles tendon attach, resulting in pain when walking (2). A rarer peripheral manifestation is dactylitis (swelling of fingers or toes).

Additionally, patients may experience extra-articular symptoms (those not related to the musculoskeletal system (30)). The most common extra-articular manifestation is uveitis, with rarer symptoms including psoriasis and IBD, both of which are associated with substantial negative impacts on quality of life (2, 31, 32). Other symptoms may include inflammation of rib joints and osteoporosis (10).

B.1.3.6 Clinical and economic burden and quality of life

Disease activity and functional impairment in nr-axSpA is comparable with that observed in patients with AS (3, 4). Symptoms limit physical functioning, including the ability to perform activities of daily living, such as dressing, walking, bathing, and eating (33).

Fatigue is a key contributor to reduced quality of life in nr-axSpA patients. The characteristic chronic low back pain that is not resolved by rest causes severe fatigue in more than half of nr-axSpA patients (34), and pain and stiffness results in poor sleep quality that also contributes to fatigue. In one study, 46% of axSpA patients reported having moderate to severe insomnia (35).

axSpA commonly starts in the second to third decade of life (36), coinciding with the start of young adults' working lives, and therefore the disease can have a considerable impact on careers, relationships and social interactions (37).

The economic impact of work limitations related to axSpA is substantial and is compounded by the typically young age at diagnosis. A cross-sectional, multi-national survey of patients with nr-axSpA and their rheumatologists conducted in France, Germany, Italy, Spain and the UK assessed the economic burden from the employer perspective. In 2014, productivity losses for employers in these countries

was reported at €10,834.92 per biologic-untreated nr-axSpA patient over a 6-month period (38).

Substantial work productivity loss has been reported in patients with nr-axSpA and AS in various studies. Slightly higher and statistically significant presenteeism (32.6% vs 24.2%; p=0.02) and daily activity impairment (37% vs 29%; p=0.04) are reported in patients with nr-axSpA compared with patients with AS, respectively (4). Additionally, significantly higher sick leaves, work-loss days and work productivity loss are observed in nr-axSpA patients compared with the general population (38, 39).

B.1.3.7 Guidelines for diagnosis and treatment

Treatment goals in nr-axSpA are focused on symptom alleviation, physical function improvement, and structural damage prevention. To date no treatments have been shown to be effective in achieving complete remission or halting progression to AS (40).

The following guidelines for diagnosis and treatment are summarised below. Note that both guidelines refer to axSpA as a whole.

- “NICE guideline 65 (NG65) – Spondyloarthritis in over 16s: diagnosis and management” (41)
- “BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics” (1)

B.1.3.7.1 *Referral and diagnosis*

NG65 states that patients with suspected axSpA should be referred to a hospital rheumatologist by their general practitioner (GP) for further investigation if they meet all three criteria detailed in Table 3. If they do not meet the criteria but clinical suspicion of axSpA remains, they are advised to seek repeat assessment if new signs, symptoms or risk factors listed in Table 3 develop.

Table 3: Criteria for referral of patients with suspected axSpA

1	The patient has low back pain that started before the age of 45 years
2	This has lasted for longer than 3 months
3	Four or more of the following criteria are met (or three plus a positive HLA-B27 test): • low back pain that started before the age of 35 years • waking during the second half of the night because of symptoms • buttock pain • improvement with movement • improvement within 48 hours of taking NSAIDs • a first-degree relative with spondyloarthritis • current or past arthritis • current or past enthesitis • current or past psoriasis

Source: NICE guideline 65 – Spondyloarthritis in over 16s: diagnosis and management (41).
Abbreviations: HLA, human leukocyte antigen; NSAID, non-steroidal anti-inflammatory drug.

In specialist care settings, clinicians are advised to consider using validated spondyloarthritis criteria to guide clinical judgement when diagnosing spondyloarthritis, including ASAS criteria (axial; Figure 2), Berlin, Rome and Modified New York (41).

NG65 recommends that conventional radiography (X-ray) is performed first, with subsequent MRI investigation if the initial investigation rules out AS due to lack of structural changes visible on X-ray. However, it is becoming more common in UK clinical practice for MRI to be used as the preferred imaging assessment leading to a clinical diagnosis of axSpA. Market research indicates that in almost two thirds of cases MRI is amongst the initial imaging tests ordered (6).

Imaging is a key component of the diagnostic toolkit, but it is possible to diagnose nr-axSpA using the clinical arm of the ASAS criteria; the presence of sacroiliitis on MRI and HLA-B27 positivity are both associated with 90% sensitivity and specificity for early axSpA diagnosis (42). NG65 states that if ASAS/OMERACT MRI criteria are not met then further investigation (e.g. specialist musculoskeletal radiology review and HLA-B27 testing) is recommended (11).

B.1.3.7.2 *Treatment with NSAIDs and physiotherapy*

NG65 states that the first pharmacological option for people with pain associated with axSpA is treatment with NSAIDs. These should be prescribed at the lowest

effective dose, and consideration should be given to appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment (41).

NSAIDs are highly effective in reducing back pain and stiffness, however if NSAIDs taken at the maximum tolerated dose for 2–4 weeks do not provide adequate pain relief, patients should be switched to another NSAID (41).

In addition to pharmacological management, individuals with axSpA should be referred to a specialist physiotherapist to start an individualised, structured exercise programme (41).

Conventional disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX), sulfasalazine, or leflunomide, are generally not effective in the treatment of axSpA, but they might have a limited role for the treatment of peripheral manifestations (43).

B.1.3.7.3 *Treatment with TNFα inhibitors*

For patients with nr-axSpA, NICE guidelines state that if NSAID treatment does not result in an adequate response, or patients cannot tolerate these, TNFα inhibitors golimumab (TA497) and adalimumab, certolizumab pegol and etanercept (TA383) are recommended (Table 4).

Table 4: Summary of NICE guidelines

Guideline (Year)	Treatment	Recommendations
TA383 (2016)	• Adalimumab • Certolizumab pegol • Etanercept	Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorisations, as options for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.
TA497 (2018)	Golimumab	Golimumab is recommended, within its marketing authorisation, as an option for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs.

TNFα inhibitor therapy is effective at reducing disease activity and spinal pain in nr-axSpA, but evidence for the role of TNFα inhibitor therapy on radiographic disease progression is currently limited (1).

The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available, which may include considering associated conditions such as extra-articular manifestations (1, 41).

Both TA383 (16) and TA497 (44) state that response should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:

- a reduction in the BASDAI score to 50% of the pre-treatment value or by 2 or more units; and
- a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

Treatment with another TNFα inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNFα inhibitor, or whose disease has stopped responding after an initial response.

British Society of Rheumatology guidelines recommend that patients are treated with a TNFα inhibitor if they have active disease, defined as a BASDAI and spinal pain VAS score ≥4 despite having taken two NSAIDs for at least two weeks each. BASDAI should be measured on two occasions at least four weeks apart, with the aim of avoiding the overtreatment of patients with short-lived disease flares (1). This compares with 12 weeks recommended by NICE but is stated to be sufficient because flares last on average 2–3 weeks.

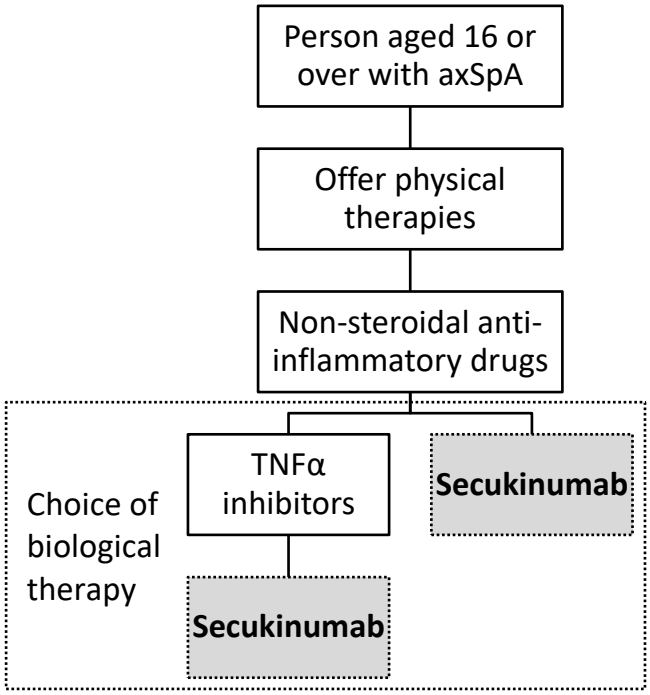
The guidelines state that response should be assessed following 3–6 months of therapy, with subsequent assessments every six months. The definition of response differs from the one used by NICE: a reduction in BASDAI and spinal pain VAS ≥ 2 units from baseline. The TNFα inhibitor should be withdrawn if there is an absence of response by six months, or failure to maintain response at two consecutive assessments.

B.1.3.8 Proposed pathway of care

The pathway of care according to NG65, modified to include the proposed positioning of secukinumab, is presented in Figure 2. It is anticipated that secukinumab will be used within its licensed indication, for treating active nr-axSpA

with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence in adults who have responded inadequately to NSAIDs.

Figure 4: NICE guideline for managing spondyloarthritis (including proposed positioning of secukinumab)



Abbreviations: axSpA, axial spondyloarthritis; TNFα, tumour necrosis factor alpha.

B.1.3.9 Unmet need

For patients who have not responded to, or who cannot tolerate, NSAIDs, TNFα inhibitors are currently the only class of drugs recommended by NICE for treating nr-axSpA. There remains a significant unmet need for new treatment options due to limitations in treatment efficacy (Section B.1.3.9.1), safety (Section B.1.3.9.2) and impact on quality of life (Section B.1.3.9.3) with TNFα inhibitors.

As an inhibitor of IL-17A, a key cytokine in the pathogenesis of SpA (Section B.1.3.4), secukinumab offers a new mode of action for patients with nr-axSpA, for whom TNFα inhibitors are the only currently recommended treatment option.

B.1.3.9.1 *Suboptimal efficacy of TNFα inhibitors*

More than 60% of patients treated with TNFα inhibitors do not achieve an ASAS40 response[b] (45-51). Lack of efficacy with TNFα inhibitor treatment is the most common reason for treatment discontinuation and treatment switching in patients with nr-axSpA (52, 53). Data from a cross-sectional, multi-national survey of 1,995 nr-axSpA patients and their rheumatologists revealed that of the 114 patients with known reasons for switching from their previous biologic, 35% switched due to loss of initial response, in 33% their condition worsened, in 25% remission was not achieved, and 24% switched due to poor pain control (54).

B.1.3.9.2 *Long-term safety issues with TNFα inhibitors*

One of the major risks of using TNFα inhibitors is the small but significant risk of serious opportunistic infections, as TNFα plays a number of key roles in the regulation of a healthy immune system (52). Findings from a meta-analysis suggest that the risk of tuberculosis may be significantly increased in patients treated with TNFα inhibitors, and this necessitates monitoring during and after treatment (55). Adalimumab and etanercept are also associated with new onset or exacerbation of central nervous system demyelinating disease (e.g. multiple sclerosis) and are contraindicated or include warnings for patients with moderate to severe heart failure (56, 57).

B.1.3.9.3 *Quality of life*

As discussed in Section B.1.3.6, fatigue is a major contributor to reduced quality of life in nr-axSpA patients. In axSpA fatigue remains unresponsive to TNFα inhibitor in nearly 80% of patients (34). In AS patients, secukinumab has been shown to provide rapid and sustained relief of fatigue over two years as measured on the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale (58, 59).

B.1.4 Equality considerations

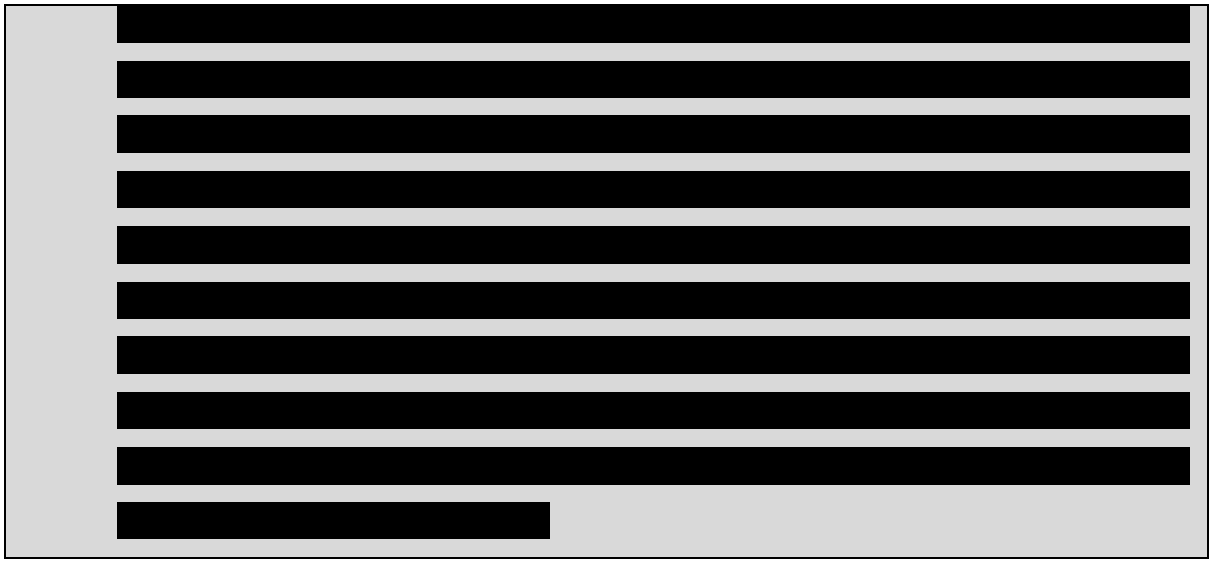
No equality issues have been identified.

[b] Defined as an improvement of ≥40% and ≥2 units on a scale of 10 in at least 3 of the 4 main domains and no worsening at all in the remaining domain.

B.2 Clinical effectiveness

The PREVENT RCT in patients with active nr-axSpA showed that secukinumab 150 mg was associated with improved outcomes vs placebo

- One RCT of secukinumab (PREVENT) was identified in 555 patients with active nr-axSpA. Trial arms were:
  - Secukinumab 150 mg No Load (secukinumab every four weeks)
  - Secukinumab 150 mg Load (secukinumab every four weeks, and with additional loading doses at Weeks 1, 2 and 3)
  - Placebo
- In the PREVENT trial, secukinumab 150 mg was associated with improved clinical outcomes vs placebo
  - At 16 weeks, TNFα-naïve patients with nr-axSpA treated with secukinumab 150 mg Load and secukinumab 150 mg No Load achieved a statistically significantly better ASAS40 response than placebo
    - secukinumab 150 mg Load (41.5%) vs placebo (29.2%), p=0.0197
    - secukinumab 150 mg No Load (42.2%) vs placebo (29.2%), [redacted]
  - At 16 weeks, the full cohort of patients with nr-axSpA treated with secukinumab 150 mg Load and secukinumab 150 mg No Load achieved a statistically significantly better ASAS40 response than placebo
    - secukinumab 150 mg Load (40.0%) vs placebo (28.0%), [redacted]
    - secukinumab 150 mg No Load (40.8%) vs placebo (28.0%), [redacted]
  - Statistically significantly better results compared with placebo were also achieved by patients with nr-axSpA treated with secukinumab 150 mg Load and secukinumab 150 mg No Load for outcomes of [redacted], BASDAI change from baseline, BASDAI50 response, hsCRP change from baseline, BASFI change from baseline, MRI SI joint oedema score change from baseline, [redacted], SF-36 PCS and [redacted] change from baseline, ASQoL change from baseline, and ASAS partial remission
  - **The NMA showed that**
    [redacted]



B.2.1 Identification and selection of relevant studies

The clinical systematic literature review (SLR) of publicly available resources did not identify any studies of secukinumab in patients with nr-axSpA (60). However, one internal document (the clinical trial report (61) for the PREVENT randomised controlled trial [RCT]) was identified from company resources and is used to present the clinical evidence for secukinumab. Appendix D contains the full details of the process and methods used in the clinical SLR.

B.2.2 List of relevant clinical effectiveness evidence

The PREVENT study provides clinical effectiveness evidence for secukinumab at its licensed dosage (150 mg) and within the indication being appraised (people with nr-axSpA with objective signs of inflammation, whose disease has responded inadequately to, or who are intolerant to, NSAIDs). Details of this study are provided in Table 5.

Table 5: Clinical effectiveness evidence

Study	PREVENT (NCT02696031)				
Study design	Randomised, double-blind, placebo-controlled, Phase III trial				
Population	Adult patients fulfilling the ASAS classification criteria for axSpA plus an abnormal CRP and/or MRI†, with no radiographic evidence of changes in the sacroiliac joints that would meet the modified New York criteria for AS				
Intervention(s)	Secukinumab Q4W (with or without loading)				
Comparator(s)	Placebo				
	Yes	✓		Yes	✓

Indicate if trial supports application for marketing authorisation	No		Indicate if trial used in the economic model	No	
Rationale for use/non-use in the model	Pivotal trial comparing the efficacy and safety of secukinumab against placebo. The trial is used in the meta-analysis to assess relative efficacy vs the comparators listed in the NICE scope.				
Reported outcomes specified in the decision problem	**Disease activity** **Functional capacity** Disease progression Pain Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) **Adverse effects of treatment** **Health-related quality of life**				
All other reported outcomes	Use of concomitant medications, pharmacokinetics, pharmacodynamics, biomarker identification, exploratory pharmacogenetic assessments				

†Following MRI, images were transferred to the central imaging lab for central (independent) review to ensure consistency and specificity of nr-axSpA diagnoses.
Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; axSpA, axial spondyloarthritis; CRP, C-reactive protein; MRI, magnetic resonance imaging; Q4W, every four weeks; vs, versus.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

PREVENT (NCT02696031) is a Phase III, randomised, double-blind, placebo-controlled, multi-centre study, which evaluated the efficacy and safety of two different secukinumab regimens (without and with loading) vs placebo in the treatment of adult patients with active nr-axSpA.

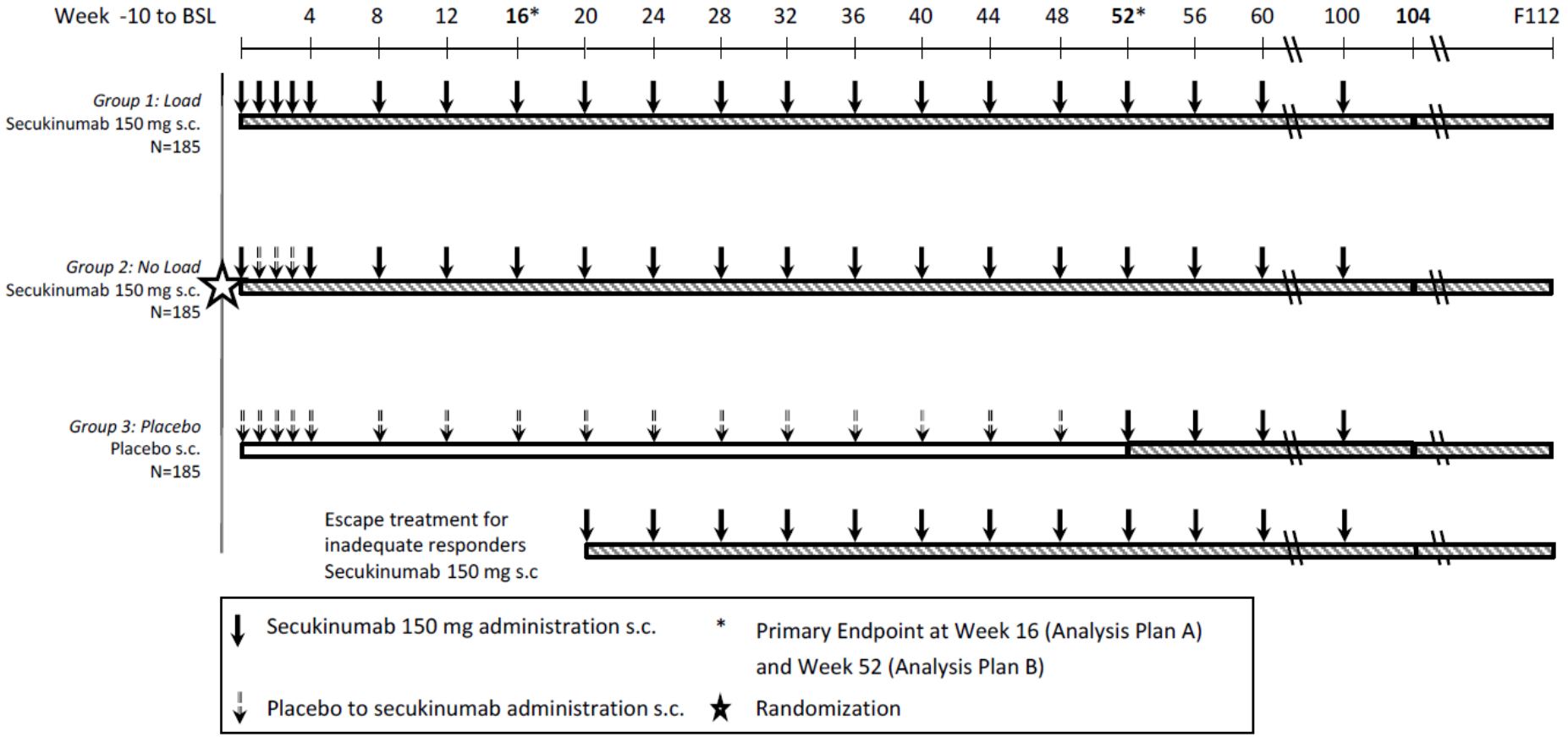
The trial has two primary endpoints, to fulfil European Medicines Agency (EMA) and US Food and Drug Administration (FDA) criteria. The primary endpoint for the EMA (analysis plan A) was to demonstrate superiority of secukinumab 150 mg subcutaneous (SC) with loading over placebo in ASAS40 response in TNFα-naïve patients at Week 16. The primary endpoint for the FDA (analysis plan B) was to demonstrate superiority of secukinumab 150 mg SC without loading over placebo in ASAS40 response in TNFα-naïve patients at Week 52.

The PREVENT trial is currently ongoing. This submission presents the results of the EMA analysis at 16 weeks as the primary analysis, using data from an interim

database lock when all patients had completed 24 weeks of the trial. Results of the interim analysis at 52 weeks are also presented in Sections B.2.6.18 to B.2.6.20.

Figure 5 presents a study timeline.

Figure 5: Study design



Source: PREVENT protocol
Abbreviations: BSL, baseline; s.c. subcutaneous.

From Week 52, all patients who had not discontinued were permitted to receive open label secukinumab 150 mg. A placebo-controlled period of 52 weeks was considered the shortest possible timeframe to assess differences in effects on signs of structural damage (assessed by MRI) between both treatment groups.

All patients were followed up 12 weeks after last administration of study treatment, regardless of discontinuation status.

Some exploratory endpoints in PREVENT include assessments at Week 104, and so will not be available until Q4 2020.

B.2.3.2 Randomisation

At baseline, all eligible patients were randomised in a 1:1:1 ratio to one of three treatment arms (secukinumab 150 mg Load, secukinumab 150 mg No Load, or placebo) via interactive response technology. Patients were stratified according to objective signs of inflammation (CRP and MRI status: CRP+ and MRI+, CRP+ and MRI–, CRP– and MRI+) at screening, with no less than 15% of patients belonging to each of the three subgroups.

B.2.3.3 Blinding

PREVENT was a double-blind study with treatment assignment concealed from patients and investigators. Treatment assignment remained blinded until all patients completed the Week 52 visit.

B.2.3.4 Eligibility criteria

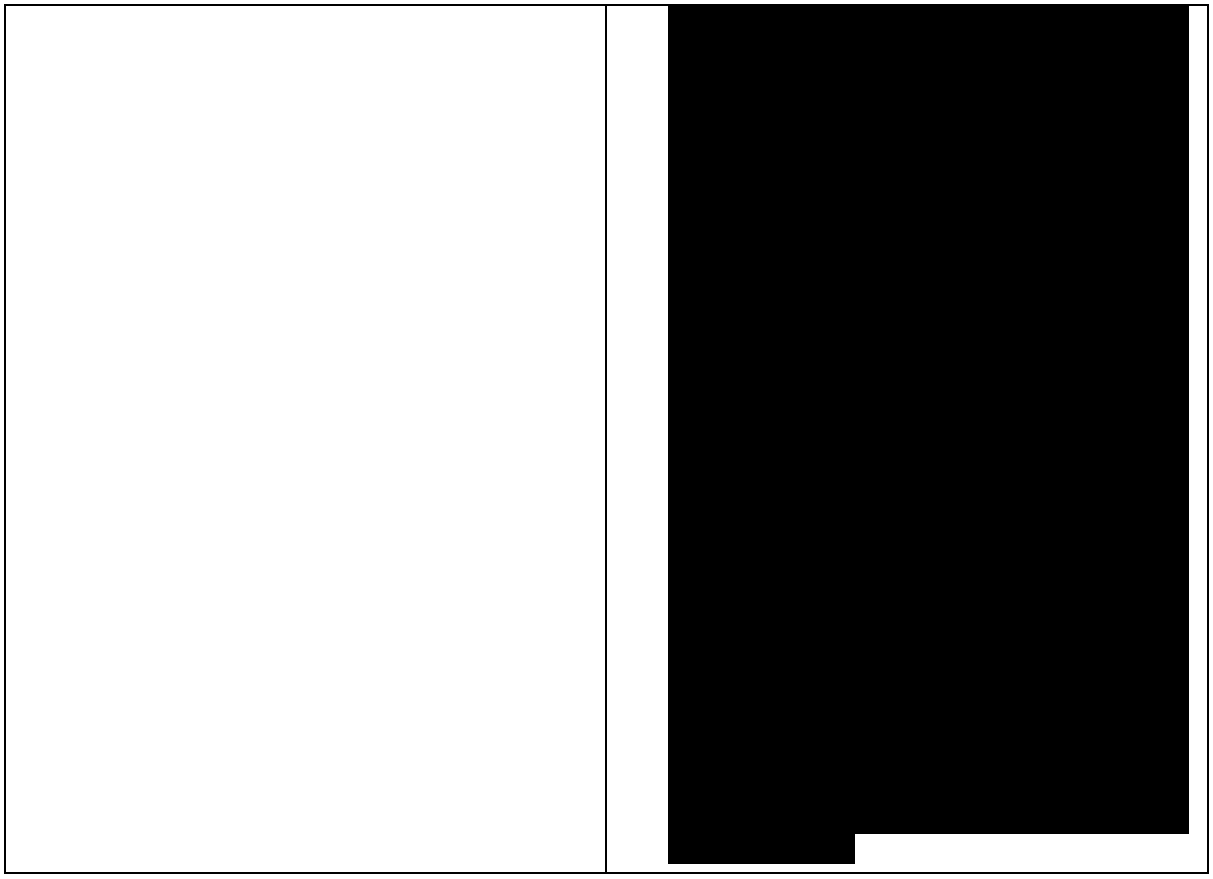
Key inclusion and exclusion criteria are presented in Table 6.

Table 6: Key eligibility criteria in PREVENT

Inclusion criteria	Exclusion criteria

• Male or non-pregnant, non-nursing female patients ≥18 years of age
• Diagnosis of axSpA according to ASAS axSpA criteria:
  ○ Inflammatory back pain for ≥6 months
  ○ [redacted]
• Objective signs of inflammation at screening, evident by either MRI with
	• Radiographic evidence for sacroiliitis, grade ≥2 bilaterally or grade ≥3 unilaterally (radiological criterion according to the modified New York diagnostic criteria for AS)
	• Inability or unwillingness to undergo MRI
	• Chest X-ray or MRI with evidence of ongoing infectious or malignant process within 3 months of screening
	• Use of high potency opioid analgesics

sacroiliac joint inflammation and/or hsCRP >ULN • Active axSpA as assessed by BASDAI ≥ 4 cm (0–10 cm) at baseline • Spinal pain as measured by BASDAI question #2 ≥4 cm (0–10 cm) at baseline • Total back pain as measured by VAS ≥40 mm (0–100 mm) at baseline • [redacted] • Patients who have been on a TNFα inhibitor (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for ≥3 months prior to randomisation or have been intolerant to at least one administration of an anti-TNFα agent • [redacted]	• Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor • [redacted] • Active ongoing inflammatory diseases other than axSpA that might confound the evaluation of the benefit of secukinumab therapy, including IBD or uveitis • [redacted]



Abbreviations: AS, ankylosing spondylitis; ASAP, as soon as possible; ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BCC, basal cell carcinoma; CHF, congestive heart failure; COX, cyclooxygenase; DMARD, disease modifying anti-rheumatic drug; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; hsCRP, high sensitivity C-reactive protein; IBD, inflammatory bowel disease; IL-17, interleukin 17; IM, intramuscular; MRI, magnetic resonance imaging; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; NYHA, New York Heart Association; PFS, pre-filled syringe; SCr, serum creatinine; TB, tuberculosis; TNFα, tumour necrosis factor alpha; ULN, upper limit of normal; VAS, visual analogue score; WBC, white blood cell.

B.2.3.5 Settings and locations where the data were collected

The PREVENT study took place at 140 investigative sites across 24 countries, including nine sites in the UK. In total, 24 patients were randomised in the UK.

B.2.3.6 Trial drugs and concomitant medications

B.2.3.6.1 *Intervention*

The intervention was secukinumab 150 mg provided in a 1 mL pre-filled syringe (PFS). This dose was selected based on dose-efficacy relationships observed in a proof of concept trial (NCT00809159) (62) and two Phase III trials in patients with AS (NCT01358175, NCT01649375) (63). There were two intervention groups (one with a loading dose and one without) to enable assessment of the impact of the loading regimen itself and to reflect flexibility of the dosing requirement in the US:

- Secukinumab 150 mg Load
    - Secukinumab 150 mg at baseline, Weeks 1, 2 and 3, and every 4 weeks starting at Week 4
- Secukinumab 150 mg No Load
    - Secukinumab 150 mg at baseline with placebo at Weeks 1, 2 and 3, followed by secukinumab 150 mg every 4 weeks starting at Week 4.

B.2.3.6.2 *Comparator*

The comparator was placebo, also provided in a 1 mL PFS, administered at baseline, Weeks 1, 2 and 3, and every 4 weeks starting at Week 4. A placebo arm was considered necessary to obtain reliable efficacy measurements due to the nature of the disease and the outcome measures used.

B.2.3.6.3 *Administration of intervention and comparator treatments*

Patients were instructed by site staff on self-administration of the SC injection using the PFS, and treatment was administered by the patient under the supervision of site staff until Week 52. After Week 52, patients were allowed to self-administer at home. Patients who were not comfortable self-injecting were injected by site staff or caregivers.

B.2.3.6.4 *Concomitant medications*

From Week 16, background medications such as NSAIDs and DMARDs could be modified or added to treat signs and symptoms of nr-axSpA. Patients who were considered inadequate responders on two or more consecutive visits were permitted to receive secukinumab or other biologics as standard-of-care (SoC) from Week 20.

Trial guidelines on the use of specific concomitant treatments are described in Table 7.

Table 7: Concomitant treatment guidance

Treatment	Guidance
Methotrexate	Patients taking MTX (≤25 mg/week) were to be on a stable dose for ≥4 weeks before randomisation and maintained on a stable dose until Week 16
Folic acid	Patients on MTX were to take folic acid supplementation before randomisation and during the trial to minimise the likelihood of MTX associated toxicity

Sulfasalazine	Patients taking sulfasalazine (≤3 g/day) were to be on a stable dose for ≥4 weeks before randomisation and maintained on a stable dose until Week 16
Leflunomide wash-out with cholestyramine	In case of leflunomide treatment, a drug wash-out of 8 weeks was performed. After all Week 16 assessments were completed, leflunomide therapy could be initiated as a background medication
Systemic corticosteroids	Treatment with systemic corticosteroids was permitted if the dose was stable within the 2 weeks preceding randomisation, up to a maximum daily dosage of 10 mg prednisone equivalent. After Week 16, the dose and regimen of systemic corticosteroids could be modified as per investigator's judgment and patient's need, although the corticosteroid dose should not be reduced rapidly. Intra-articular corticosteroids were not permitted within the 4 weeks preceding randomisation and up to Week 16. No single injection should exceed 40 mg of triamcinolone (or equivalent) and the total dose of intra-articular corticosteroid may not exceed 80 mg of triamcinolone (or equivalent) during any 52-week period. Injection of intra-articular steroids was not permitted within 8 weeks prior to Week 52.
NSAIDs (including COX-1 or COX-2 inhibitors) and acetaminophen/paracetamol	Patients on regular use of NSAIDs or paracetamol/acetaminophen should have been on stable dose for at least 2 weeks before randomisation to allow inclusion in the study NSAIDs, low strength opioids or paracetamol/acetaminophen PRN could be taken during the study; however, patients should refrain from any intake during ≥24 hours before a visit with disease activity assessment After the Week 16 assessments were completed, a change in the NSAID intake regimen was permitted.
TNFα inhibitors	If TNFα inhibitors were chosen as escape treatment for patients considered as inadequate responders, a 12-week wash out period was to be observed after administration of the last dose of blinded study treatment for safety reasons. Thus, the earliest time for the patient to receive the TNFα inhibitor was at Week 28. TNFα inhibitors prescribed in accordance with investigator practice, treatment guidelines or locally approved uses were not considered study medication and were not be supplied by the sponsor.

Abbreviations: COX, cyclooxygenase; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PRN, pro re nata; TNFα, tumour necrosis factor alpha.

B.2.3.7 Outcomes specified in the scope

Outcomes specified in the scope relate to primary, secondary and exploratory endpoints in the trial. Primary and secondary trial outcomes (analysis plan A – Section B.2.3.1) are listed below.

B.2.3.7.1 *Primary outcome*

The primary outcome was the proportion of TNFα-naïve patients achieving an ASAS40 response at Week 16. Secondary endpoints included assessment of all patients, and exploratory analyses allowed for the assessment of responses in

TNFα-naïve and tumour necrosis factor inadequate response (TNF-IR) subpopulations.

B.2.3.7.2 *Other outcomes used in the economic model/specified in scope*

Secondary trial endpoints related to outcomes specified in the scope are presented in Table 8, together with cross-references to the sections where results are presented.

Table 8: Other outcomes

Outcome specified in the scope	Trial endpoints
Disease activity	• ASAS40 (Sections B.2.6.4, B.2.6.5), ASAS 5/6 (Section B.2.6.6), ASAS20 (Section B.2.6.12), and ASAS partial remission (Section B.2.6.15) • BASDAI (Section B.2.6.7), BASDAI50 (Section B.2.6.8) • Change in hsCRP (Section B.2.6.9) • Patient's global assessment of disease activity (component of ASAS) (Section B.2.6.17) • Inflammation as measured by the mean of BASDAI questions 5 and 6 (component of ASAS) (Section B.2.6.6) • Change in ASDAS-CRP (Section B.2.6.17) and ASDAS-ESR (Section B.2.6.17) • Change in ESR (Section B.2.6.17)
Functional capacity	• Change in BASFI (Section B.2.6.10) • Spinal mobility assessed by BASMI linear scores (Section B.2.6.17)
Disease progression	• Change in SI joint oedema on MRI (Section B.2.6.11) • Change in spine oedema score on MRI • Change in total quadrant level fatty lesions in SI joint and spine†
Pain	• Total spinal pain (component of ASAS) (Section B.2.6.17) • Change in nocturnal back pain‡
Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis)	• MASES (Section B.2.6.17) • Change in tender or swollen joint count as determined by the 44-joint assessment (Section B.2.6.17)
Symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis)	Not applicable – These are not measured outcomes within PREVENT
Adverse effects of treatment	• Overall safety and tolerability (Section B.2.10)
Health-related quality of life	• Change in SF-36 PCS (Section B.2.6.13) • Change in ASQoL (Section B.2.6.14) • SF-36 (Section B.2.6.16.2) • FACIT-Fatigue (Section B.2.6.16.4)

	• EQ-5D (Section B.2.6.16.5) • WPAI-GH (Section B.2.6.17)

†Not yet assessed – to be assessed at final MRI reading; ‡Not yet assessed – to be added to final clinical trial report.
Abbreviations: ASQoL, Ankylosing Spondylitis Quality of Life; ASAS, Assessment of SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; EQ-5D, EuroQol 5 dimensions; FACIT, Functional Assessment of Chronic Illness Therapy; hsCRP, High sensitivity C-reactive protein; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MRI, magnetic resonance imaging; mSASSS, Modified Stoke Ankylosing Spondylitis Spinal Score; SF-36, 36-Item Short Form Survey; SI, sacroiliac; WPAI-GH, Work Productivity and Activity Impairment Questionnaire – General Health.

B.2.3.8 Baseline characteristics

Details of baseline characteristics are provided in Table 9. Baseline demographics and disease characteristics were well balanced across treatment groups. Mean age was 39.4 years, mean body mass index (BMI) was [redacted] kg/m^2, and there were more female (54.1%) than male (45.9%) patients. Overall, patients had a mean time since onset of back pain of 8.56 years and a mean time since first diagnosis of axSpA of [redacted] years. [redacted]
The majority of patients (90.3%) were naïve to TNFα inhibitors, and 9.7% of patients had received one prior TNFα inhibitor with inadequate response or intolerance.

Table 9: Baseline characteristics

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Placebo N=186	Total N=555
Demographics				
Age, years, mean ± SD	39.1 ± 11.45	39.8 ± 11.68	39.3 ± 11.47	39.4 [redacted]
Gender, female, n (%)	105 (56.8)	100 (54.3)	95 (51.1)	[redacted]
Race, n (%) American Indian or Alaska Native Asian Black or African American White Other	[redacted]	[redacted]	[redacted]	[redacted]
BMI, kg/m^2 n Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Disease indicators				
Time since diagnosis, years, mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Placebo N=186	Total N=555
Time since onset of back pain, years				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	8.724 ± 9.2659	8.573 ± 8.6355	8.385 ± 8.3413	8.56[redacted]
Patient's global assessment of disease activity (0–100 mm)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Total back pain (0–100 mm), mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Nocturnal back pain (0–100 mm), mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
MASES, mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Erythrocyte sedimentation rate (mm/h)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
hsCRP (mg/L), mean ± SD	13.17 ± 27.209	9.67 ± 15.815	10.76 ± 21.335	[redacted]
Abnormal hsCRP, n (%)	104 (56.2)	107 (58.2)	105 (56.5)	[redacted]
Sacroiliac joint inflammation on MRI by history or current, n (%)	132 (71.4)	134 (72.8)	139 (74.7)	[redacted]
CRP and MRI status, n (%)				
CRP+ and MRI+	[redacted]	[redacted]	[redacted]	[redacted]
CRP+ and MRI–	[redacted]	[redacted]	[redacted]	[redacted]
CRP– and MRI+	[redacted]	[redacted]	[redacted]	[redacted]
HLA-B27, n (%)				
Negative	[redacted]	[redacted]	[redacted]	[redacted]
Positive	136 (73.5)	117 (63.6)	129 (69.4)	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Naïve to TNFα inhibitors, n (%)	21 (11.4)	18 (9.8)	15 (8.1)	[redacted]

Abbreviations: BMI, body mass index; CRP, c-reactive protein; CRP+, patient with a CRP value above the ULN at screening; CRP–, patient with a CRP value below the ULN at screening; HLA, human leukocyte antigen; hsCRP, high sensitivity c-reactive protein; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MRI, Magnetic resonance imaging; MRI+, Patient with an MRI considered positive for sacroiliitis at screening; MRI–, Patient with an MRI considered negative for sacroiliitis at screening; NSAIDs, non-steroidal

anti-inflammatory drug; SD, standard deviation; TNFα, tumour necrosis factor alpha; VAS, visual analogue score.

Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Metrology Index (BASMI) characteristics at baseline were similar across treatment groups, with an overall mean BASFI score of [redacted], a mean BASDAI score of [redacted] and a mean BASMI (linear) score of [redacted] (Table 10).

Table 10: Baseline BASFI, BASDAI and BASMI

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Placebo N=186	Total N=555
BASFI				
Mean ± SD	6.244 ± 2.0392	5.922 ± 2.0345	5.893 ± 1.8998	[redacted]
BASDAI				
Mean ± SD	7.082 ± 1.3307	6.931 ± 1.4494	6.760 ± 1.2422	[redacted]
Spinal Pain (BASDAI Question#2)				
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
BASMI (linear)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
BASMI – lateral spinal flexion (cm)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
BASMI – tragus to wall distance (cm)				
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
BASMI – lumbar flexion (modified Schober, cm)				
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
BASMI – maximal intermalleolar distance (cm)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
BASMI – cervical rotation angle (degrees)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
BASMI – chest expansion (cm)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Placebo N=186	Total N=555
BASMI – occiput-to-wall distance (cm)				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; SD, Standard deviation.

In total, [redacted] of all patients used methotrexate (mean dose of [redacted]), [redacted] used sulfasalazine (mean dose of [redacted]), and [redacted] used corticosteroids (mean dose of [redacted]), with similar proportions of patients across treatment groups. Treatment groups were balanced in terms of cardiovascular history. [redacted] patients across treatment groups had at least one relevant medical history or current medical condition, with no clinically meaningful differences between treatment groups ([redacted] in the secukinumab 150 mg Load group, [redacted] in the secukinumab 150 mg No Load group, and [redacted] in the placebo group).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis sets

The following analysis sets were defined in the trial:

- **Randomised set:** The randomised set was defined as all patients who were randomised. Unless otherwise specified, mis-randomised patients (mis-randomised into the interactive response technology [IRT]) were excluded from the randomised set. Mis-randomised patients were defined as those patients who were mistakenly randomised into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomised patients were treated as screen failures.
- **Full analysis set (FAS):** The FAS was comprised of all analysable patients from the randomised set to whom study treatment had been assigned.

Following the intent-to-treat principle, patients were evaluated according to the treatment assigned at randomisation, but actual stratum[c].

- **Full analysis set 2 (FAS2):** The FAS2 was comprised of all patients from the randomised set to whom study treatment had been assigned and who had been in enrolled at least 379 days (upper limit of visit window for Analysis Plan B primary endpoint) before date cut-off. Following the intent-to-treat principle, patients were evaluated according to the treatment assigned at randomisation, but actual stratum[c].
- **Safety set:** The safety set included all patients who took at least one dose of study treatment during the treatment period. Patients were evaluated according to treatment received.

B.2.4.2 Statistical information

A summary of the statistical methods used in PREVENT is provided in Section B.2.4.2.1 to Section B.2.4.2.5.

B.2.4.2.1 *Hypothesis objective*

To demonstrate that secukinumab 150 mg SC (with load) at Week 16 was superior to placebo in TNFα-naïve patients with active nr-axSpA based on the proportion of patients achieving an ASAS40 response.

B.2.4.2.2 *Statistical analysis of primary endpoints*

The analysis of the primary variable was based on the FAS. The statistical hypothesis for ASAS40 being tested was that there is no difference in the proportion of TNFα-naïve patients fulfilling the ASAS40 criteria at Week 16 in the secukinumab 150 mg Load regimen vs placebo regimen.

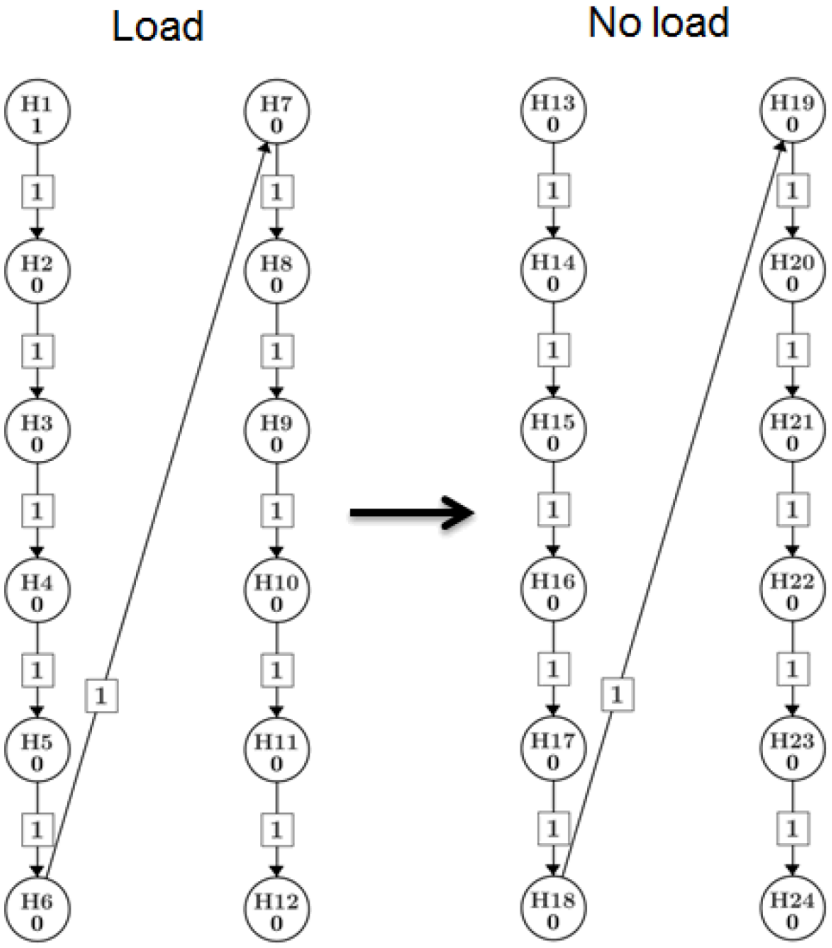
The primary analysis was conducted via logistic regression with treatment and stratification factor (CRP+/MRI+, CRP+/MRI–, CRP–/MRI+) as factors and weight as a covariate. Odds ratios and 95% confidence intervals (CI) were presented comparing each secukinumab regimen to placebo.

[c] Where patients were assigned to the wrong CRP/MRI stratification group at the study site, stratification group was overwritten by actual stratum.

B.2.4.2.3 ***Statistical analysis of secondary endpoints***

Secondary efficacy variables were analysed using the FAS population. The family-wise error was set to α=5% and it was controlled with the proposed sequential testing strategy as described in Figure 6.

Figure 6: Testing strategy for Analysis Plan A



The primary hypothesis (H1) for the primary objective (ASAS40 in TNFα-naïve patients at Week 16) for secukinumab with load regimen vs placebo was tested at α-level. If the hypothesis H1 was rejected, then the whole was passed to the next hypothesis (H2) which was tested at α-level. This procedure continued (pending rejection of the null hypotheses) until H12 was rejected. If H12 was rejected, then the full α-level was passed on to the testing sequence of secukinumab without load which could now be tested at 5% level sequentially in a similar way.

Of note, in the description above, rejection of a hypothesis referred to rejection of the two-sided hypothesis; however, the level of a rejected hypothesis was only passed

on according to the sequence for the test of another hypothesis if the treatment effect was in favour of secukinumab.

B.2.4.2.4 *Sample size and power calculation*

Assumptions made in performing sample size calculations were based on the results of a study of a TNFα inhibitor in the same indication of similar design, which reported an ASAS40 response rate of 47.1% for the active treatment and 16% for placebo at Week 12 (49). However, this trial had a limited number of TNF-IR patients and a meta-analysis (MA) from studies with secukinumab in AS indicated that the placebo rates observed in recent AS studies may be higher. Hence, assumptions were based on the result of active treatment from this TNF inhibitor study in nr-axSpA (but adjusted for the expected inclusion of TNF-IR patients) and with placebo response rates taken from the secukinumab MA. This MA included approximately 25% TNF-IR patients, and the ASAS40 response rate in the 150 mg dose for TNF-IR was 76% of the response in the TNFα-naïve group. Assuming 20% of randomised patients were TNF-IR and had the same TNF-IR vs TNF-naïve response ratio as seen in the MA (76%), the estimate for the entire population was 44.8% (i.e. 47.1%*0.8 + 47.1%*0.2*0.76) for secukinumab and 25.9% for placebo. ASAS40 in TNFα-naïve patients only was assumed to be 47.1% for secukinumab and 27.9% for placebo.

An overall type I error (2-sided) of 5% was used to control type I error. Since the hierarchy was sequential starting with secukinumab with load tested vs placebo, the full type I error was utilised for each comparison. Based on these assumptions it was calculated that including 185 patients per arm would give 91% power to reject a hypothesis of equal response rate based on Fisher's exact test.

B.2.4.2.5 *Data management, patient withdrawals*

Missing data for ASAS20/40 response and other binary efficacy variables (e.g. ASAS 5/6, etc.) for data up to Week 52 were handled as follows:

1. Patients who dropped out of the trial for any reason were considered as non-responders from the time they drop out through Week 52
2. Patients who did not have the required data to compute responses (e.g. ASAS components) at baseline and at the specific timepoint were classified as non-responders at the specific timepoint.

Patients who were unblinded were considered non-responders from the time of unblinding up to Week 52. The primary analysis used non-responder imputation. Continuous variables (e.g. ASAS components), except for MRI endpoints, were analysed using a mixed-effects model repeated measures (MMRM) which was valid under the missing at random (MAR) assumption. The MMRM models were applied only up to Week 20 when no treatment switching had occurred. As such, single-point imputation of missing data was not performed (e.g. last observation carried forward). For MMRM analyses of continuous variables, if all post-baseline values were missing, then these missing values were not imputed and this patient was removed from the analysis of the corresponding variable, i.e. it could be that the number of patients providing data to an analysis was smaller than the number of patients in the FAS.

For SI joint oedema on MRI a multiple imputation (MI) approach under MAR assumption was applied to handle missing data. The MI model included stratification factor (CRP+/MRI+, CRP+/MRI–, CRP–/MRI+) and TNFα inhibitor status as categorical covariates and patient weight as a continuous covariate.

Imputation under MAR relied on the assumption that unbiased estimates could be obtained by borrowing information from patients with collected data that were similar with regard to model baseline covariates and measurements collected at prior visits.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Appendix D contains the quality assessment of each of the trials identified in the SLR.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Patient disposition

Overall, 95.0% of randomised patients completed Week 24 of the study, with similar proportions across all three treatment groups (Table 11).

Table 11: Patient disposition

n (%)	Secukinumab 150 mg Load	Secukinumab 150 mg No Load	Placebo	Total
Screened				1,583
Randomised	185 (100)	184 (100)	186 (100)	555 (100)
FAS	185 (100)	184 (100)	186 (100)	555 (100)
SAS	[redacted]	[redacted]	[redacted]	[redacted]
Completed Week 24	175 (94.6)	177 (96.2)	175 (94.1)	527 (95.0)
Discontinued before/at Week 24	10 (5.4)	7 (3.8)	11 (5.9)	28 (5.0)
AE	2 (1.1)	4 (2.2)	2 (1.1)	8 (1.4)
Lack of efficacy	2 (1.1)	1 (0.5)	2 (1.1)	5 (0.9)
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	1 (0.5)	0	1 (0.5)	2 (0.4)
Protocol deviation	1 (0.5)	0	0	1 (0.2)
Subject/guardian decision	4 (2.2)	1 (0.5)	5 (2.7)	10 (1.8)
FAS2[†]	[redacted]	[redacted]	[redacted]	[redacted]
Completed Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Switchers between Week 20 and Week 52	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued before/at Week 52	[redacted]	[redacted]	[redacted]	[redacted]

[†]the FAS2 population comprised [redacted] patients ([redacted] of the FAS) and was used for the interim analyses of 52-week data.
Abbreviations: AE, adverse event; FAS, full analysis set; SAS, safety analysis set.

B.2.6.2 Descriptions of study assessments

Descriptions of study assessments are provided in Table 12.

Table 12: Overview of study assessments

Assessment	Description
Efficacy assessments	
Assessment of SpondyloArthritis International Society criteria (ASAS) (64)	Main ASAS domains: 1. Patient's global assessment of disease activity measured on a VAS 2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS 3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS 4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS Additional assessment domains: 5. Spinal mobility represented by the BASMI lateral spinal flexion assessment 6. C-reactive protein (acute phase reactant)

Assessment	Description
ASAS Response Criteria-20% (ASAS20)	Improvement of ≥20% and ≥1 unit on a scale of 10 in at least 3 of the 4 main domains and no worsening of ≥20% and ≥1 unit on a scale of 10 in the remaining domain
ASAS Response Criteria-40% (ASAS40)	Improvement of ≥40% and ≥2 units on a scale of 10 in at least 3 of the 4 main domains and no worsening at all in the remaining domain
ASAS 5/6 improvement criteria	Improvement of ≥20% in at least 5 of all 6 domains
ASAS partial remission criteria	Value not above 2 units in each of the 4 main domains on a scale of 10
Patient's global assessment of disease activity	Assessed using a 100 mm VAS ranging from not severe to very severe, after the question, "How active was your disease on average during the last week?"
Patient's assessment of back pain intensity (VAS)	Assessed using a 100 mm VAS ranging from no pain to unbearable pain, after the question "Based on your assessment, please indicate what is the amount of back pain at any time that you experienced during the last week?" and "Based on your assessment, please indicate what is the amount of back pain at night that you experienced during the last week?"
Bath Ankylosing Spondylitis Functional Index (BASFI)	10 questions (0–10 scale on a VAS) designed to determine the degree of functional limitation in those patients with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patients' ability to cope with everyday life (65, 66)
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	6 questions (0–10 scale on a VAS) pertaining to the 5 major symptoms of AS: fatigue, spinal pain, joint pain /swelling, areas of localised tenderness (called enthesitis, or inflammation of tendons and ligaments), morning stiffness duration, morning stiffness severity
BASDAI50	The BASDAI50 was defined as an improvement of at least 50% in the BASDAI compared with baseline
Bath Ankylosing Spondylitis Metrology Index (BASMI linear)	Uses the minimum number of clinically appropriate measurements that assess accurately axial status, with the goal to define clinically significant changes in spinal movement. Parameters include lateral spinal flexion, tragus-to-wall distance, lumbar flexion (modified Schober), maximal intermalleolar distance, cervical rotation angle. Additionally, the following assessments were to be taken: chest expansion, occiput-to-wall distance
Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and expanded enthesis sites	The MASES (67, 68) was developed from the Mander index, and includes assessments of 13 sites. Enthesitis sites included in the MASES index are 1st costochondral, 7th costochondral, posterior superior iliac spine, anterior superior iliac spine, iliac crest (all above were assessed bilaterally), and 5th lumbar spinous process
High sensitivity C-reactive protein (hsCRP)	Conducted in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment
Erythrocyte sedimentation rate (ESR)	Helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy
ASDAS-ESR, ASDAS-CRP and	Composite index to assess disease activity in AS. Parameters used for the ASDAS include spinal pain (BASDAI question 2), the patient global

Assessment	Description
ASDAS response categories	assessment of disease activity, peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 6) and CRP in mg/L (or ESR) (64, 69) ASDAS-CRP = 0.121 x total back pain + 0.110 x patient global + 0.073 x peripheral pain/swelling + 0.058 x duration of morning stiffness + 0.579 x ln(hsCRP +1) ASDAS-ESR = 0.113 x patient global + 0.293 x ESR + 0.086 x peripheral pain/swelling + 0.069 x duration of morning stiffness + 0.079 x total back pain
44-tender and swollen joint-count	The following 44 joints were assessed for tenderness and swelling: 2 sternoclavicular joints L + R, 2 acromioclavicular joints L + R, 2 shoulder joints L + R, 2 elbows L+ R, 2 wrists L + R, 10 metacarpophalangeal joints L+ R, 10 proximal interphalangeal joints L+ R (hands), 2 knees L + R, 2 ankles L+ R, 10 metatarsophalangeal joints L + R
MRI	The MRI for each patient included T1 and Short T1 Inversion Recovery (STIR) sequences of the sagittal spine (cervical, thoracic and lumbar) and oblique coronal of the pelvis including both sacroiliac joints
X-ray	The X-ray requirements include lateral views of the cervical and thoraco-lumbar spine for mSASSS scoring (bottom 1/3 of C2 through top 1/3 of T1, inclusive) and anterio-posterior view of the pelvis including visibility of both sacroiliac joints for modified New York AS determination
Quality of life assessments	
Medical Outcome Short Form Health Survey (SF-36) Version 2 (Acute Form)	The SF-36 is a widely used and extensively studied instrument to measure HRQoL among healthy patients and patients with acute and chronic conditions. It consists of 8 subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health.
Ankylosing Spondylitis Quality of Life (ASQoL)	The ASQoL is a self-administered questionnaire designed to assess HRQoL in adult patients with AS. The ASQoL contains 18 items with a dichotomous yes/no response option. A single point is assigned for each "yes" response and no points for each "no" response resulting in overall scores that range from 0 (least severity) to 18 (highest severity).
Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue©)	The FACIT-Fatigue© is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. The purpose of FACIT-Fatigue in this study was to assess the impact of fatigue on patients with nr-axSpA.
EuroQol 5D	The EQ-5D is a widely used, self-administered questionnaire designed to assess health status in adults. The measure is divided into 2 distinct sections. The first section includes one item addressing each of five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Patients rate each of these items as "no problem," "some problem," or "extreme problem." A composite health index is then defined by combining the levels for each dimension. The second section of the questionnaire measures self-rated (global) health status utilizing a vertically oriented VAS where 100 represents the "best possible health state" and 0 represents the "worst possible health state." Respondents are asked to rate their current health by placing a mark along this continuum. The recall period is "today", and the questionnaire requires approximately 5 to 10 minutes to complete.
Work Productivity and Activity Impairment -	The WPAI-GH questionnaire is an instrument to measure impairments in both paid work and unpaid work. It measures absenteeism, presenteeism as well

Assessment	Description
General Health (WPAI-GH)	as the impairments in unpaid activity because of health problem during the past seven days.
Safety assessments	
QuantiFERON TB-Gold test or PPD skin test	Either a QuantiFERON TB-Gold test or a PPD skin test had to be performed at Screening. Patients with a positive test could participate in the study if further work up (according to local practice/guidelines) established conclusively that the patient had no evidence of active tuberculosis, or if presence of latent tuberculosis was established then treatment according to local guidelines had to be initiated.
Chest X-ray or MRI	A chest X-ray or MRI at Screening (or within 3 months prior to Screening) was performed to rule out the presence of a pulmonary malignancy or infectious process tuberculosis.
Physical examination	The physical examination included the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological system.
Vital signs	Vital signs included blood pressure and pulse rate measurements after 5 minutes rest in sitting position.
Height and weight	Height in centimetres (cm) and body weight (to the nearest 0.1 kg in indoor clothing) (both without shoes) were measured.
Laboratory evaluations	These included haematology, clinical chemistry, lipid panel and urinalysis.
Electrocardiogram (ECG)	A standard 12 lead ECG was performed.
Pregnancy and assessments of fertility	All pre-menopausal women who were not surgically sterile had a serum β-hCG test (serum pregnancy test) performed at the second Screening Visit and local urine pregnancy tests.
Local tolerability (injection site reactions)	The local tolerability at the site of SC injection of the study treatment was assessed in case of any local reaction, until this had disappeared.
Tolerability of secukinumab	Tolerability was assessed by AEs, laboratory values, injection site reaction and immunogenicity.

Abbreviations: ASAS, Assessment of SpondyloArthritis International Society criteria; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; HRQoL, health-related quality of life; L, left; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MRI, magnetic resonance imaging; R, right; SC, subcutaneous; SD, Standard deviation; VAS, visual analogue scale.

B.2.6.3 Summary of hierarchical testing, Week 16

All hierarchical primary and secondary endpoints at Week 16 were met (Table 13).

Table 13: Overview of hierarchical testing, Week 16, FAS

Hypothesis number	Endpoint	Comparison vs placebo	Unadjusted p-value	Adjusted p-value (testing hierarchy)	Statistically significant
1	ASAS40 in TNFα-naïve patients at Week 16	Secukinumab 150 mg Load	0.0197	0.0197	Yes
2	ASAS40 at Week 16		0.0108	0.0197	Yes
3	ASAS 5/6 at Week 16		[redacted]	0.0197	Yes
4	BASDAI at Week 16		0.0006	0.0197	Yes
5	BASDAI50 at Week 16		0.0001	0.0197	Yes
6	hsCRP at Week 16		[redacted]	0.0197	Yes
7	BASFI at Week 16		0.0041	0.0197	Yes
8	SI joint oedema on MRI at Week 16		[redacted]	0.0197	Yes
9	ASAS20 at Week 16		0.0260	0.0260	Yes
10	SF-36 PCS at Week 16		0.0006	0.0260	Yes
11	ASQoL at Week 16		0.0008	0.0260	Yes
12	ASAS partial remission at Week 16		<0.0001	0.0260	Yes
13	ASAS40 in TNFα-naïve patients at Week 16	Secukinumab 150 mg No Load	[redacted]	0.0260	Yes
14	ASAS40 at Week 16		[redacted]	0.0260	Yes
15	ASAS 5/6 at Week 16		[redacted]	0.0260	Yes
16	BASDAI at Week 16		[redacted]	0.0260	Yes
17	BASDAI50 at Week 16		[redacted]	0.0260	Yes
18	hsCRP at Week 16		[redacted]	0.0260	Yes
19	BASFI at Week 16		[redacted]	0.0260	Yes
20	SI joint oedema on MRI at Week 16		[redacted]	0.0260	Yes
21	ASAS20 at Week 16		[redacted]	0.0260	Yes
22	SF-36 PCS at Week 16		[redacted]	0.0260	Yes
23	ASQoL at Week 16		[redacted]	0.0260	Yes
24	ASAS partial remission at Week 16		[redacted]	0.0260	Yes

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; hsCRP, high sensitivity c-reactive protein, MRI, magnetic resonance imaging; SF-36, Short Form-36; SI, sacroiliac; TNFα, tumour necrosis factor alpha.

B.2.6.4 Primary endpoint: ASAS40 response in TNFα-naïve patients

The primary efficacy variable of the study was met: secukinumab 150 mg Load was superior vs placebo for ASAS40 response in TNFα-naïve patients at Week 16 using non-responder imputation (41.5% vs 29.2%; p=0.0197) (Table 14). Secukinumab 150 mg No Load also had a statistically significantly better ASAS40 response than placebo (42.2% vs 29.2%; p=0.0146).

Table 14: Primary endpoint: ASAS40 response in TNFα-naïve patients using non-responder imputation, Week 16, FAS

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=164)	68/164 (41.5)	vs No Load	0.98	[redacted]	[redacted]
		vs placebo	1.72	[redacted]	0.0197
Secukinumab 150 mg No Load (N=166)	70/166 (42.2)	vs placebo	1.76	[redacted]	[redacted]
Placebo (N=171)	50/171 (29.2)	N/A			

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; OR, odds ratio; TNFα, tumour necrosis factor alpha.

The time course of ASAS40 response in TNFα-naïve patients is shown in Figure 7. At Weeks 2–4, ASAS40 response was slightly higher with secukinumab 150 mg Load vs secukinumab 150 mg No Load, with significance (unadjusted) vs placebo being reached by Week 3 for secukinumab 150 mg Load and Week 8 for secukinumab 150 mg No Load.

Figure 7: ASAS40 response in TNFα-naïve patients with 95% CI using non-responder imputation, Week 16, FAS

★ unadjusted p-value ≤0.05.
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; TNFα, tumour necrosis factor alpha.

Sensitivity analyses support the primary analysis of the primary endpoint (Table 15).

Table 15: Sensitivity analyses: ASAS40 response in TNFα-naïve patients, Week 16, FAS

Treatment group	n/M (%)	95% CI	Comparison	OR	p-value
Observed data					
Secukinumab 150 mg Load (N=164)	[redacted]	[redacted]	vs No Load	NR	NR
		[redacted]	vs placebo	NR	NR
Secukinumab 150 mg No Load (N=166)	[redacted]	[redacted]	vs placebo	NR	NR
Placebo (N=171)	[redacted]	N/A			

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Multiple imputation					
Secukinumab 150 mg Load (N=164)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=166)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo(N=171)	[redacted]	N/A			

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; NR, not reported; OR, odds ratio; TNFα, tumour necrosis factor alpha.

B.2.6.5 Secondary endpoint: ASAS40 response in all patients

ASAS40 response in all patients using non-responder imputation at Week 16 was statistically significantly higher in the secukinumab 150 mg Load and No Load groups compared with the placebo group (40.0% and 40.8% vs 28.0%) (Table 16).

Table 16: Secondary endpoint: ASAS40 response in all patients using non-responder imputation, Week 16, FAS

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=185)	74/185 (40.0)	vs No Load	0.98	[redacted]	[redacted]
		vs placebo	1.77	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	75/184 (40.8)	vs placebo	1.80	[redacted]	[redacted]
Placebo (N=186)	52/186 (28.0)	N/A			

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; OR, odds ratio.

The time course of ASAS40 response in all patients is shown in Figure 8. At Weeks 2–4, ASAS40 response was slightly higher with secukinumab 150 mg Load vs secukinumab 150 mg No Load, with significance (unadjusted) vs placebo being reached by Week 3 for secukinumab 150 mg Load and Week 8 for secukinumab 150 mg No Load.

Figure 8: ASAS40 response in all patients with 95% CI using non-responder imputation, Week 16, FAS

★ unadjusted p-value ≤0.05.

Sensitivity analyses support the primary analysis of the secondary endpoint (Table 17).

Table 17: Sensitivity analyses: ASAS40 response in all patients, observed data, Week 16, FAS

Treatment group	n/M (%)	95% CI
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; NR, not reported; OR, odds ratio.

B.2.6.6 Secondary endpoint: ASAS 5/6 response in all patients

ASAS 5/6 response in all patients using non-responder imputation at Week 16 was [redacted] in the secukinumab 150 mg Load and No Load groups compared with the placebo group (Table 18).

Table 18: Secondary endpoint: ASAS 5/6 response in all patients using non-responder imputation, Week 16, FAS

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=185)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	N/A			

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; OR, odds ratio.

Results for ASAS 5/6 response using observed data were [redacted] to the results using non-responder imputation ([redacted] for secukinumab 150 mg Load and [redacted] for secukinumab 150 mg No Load vs [redacted] for placebo).

B.2.6.7 Secondary endpoint: BASDAI change from baseline in all patients

Least squares (LS) mean BASDAI change from baseline was statistically significantly greater in the secukinumab 150 mg Load and No Load groups compared with placebo (−2.35 and −2.43 vs −1.46) (Table 19).

Table 19: Secondary endpoint: BASDAI change from baseline in all patients using MMRM, Week 16, FAS

Treatment group	n	Within treatment	Treatment contrast			
		LS mean change (SE)	Comparison	LS mean (SE)	95% CI	p-value
Secukinumab 150 mg Load (N=185)	181	−2.35 (0.201)	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	177	−2.43 (0.203)	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	177	−1.46 (0.205)	N/A			

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed-effect model repeated measures; n, The number of patients with measures at both baseline and the corresponding post baseline visit; N, the number of patients in each treatment group of the specified analysis set; N/A, not applicable; SE, standard error.

B.2.6.8 Secondary endpoint: BASDAI50 response in all patients

BASDAI50 response in all patients using non-responder imputation at Week 16 was statistically significantly higher in the secukinumab 150 mg Load and No Load groups compared with the placebo group (Table 20).

Table 20: Secondary endpoint: BASDAI50 response in all patients using non-responder imputation, Week 16, FAS

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=185)	69/185 (37.3)	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	69/184 (37.5)	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	39/186 (21.0)	N/A			

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; OR, odds ratio.

B.2.6.9 Secondary endpoint: hsCRP change from baseline in all patients

LS mean hsCRP change from baseline was statistically significantly greater in the secukinumab 150 mg Load and No Load groups compared with placebo (0.64 for both secukinumab groups vs 0.91 for placebo) (Table 21).

Table 21: Secondary endpoint: hsCRP change from baseline in all patients using MMRM, Week 16, FAS

Treatment group	n	Within treatment	Treatment contrast			
		Exploratory LS mean change (SE)	Comparison	LS mean (SE)	95% CI	p-value
Secukinumab 150 mg Load (N=185)	180	0.64 (1.078)	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	176	0.64 (1.079)	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	175	0.91 (1.080)	N/A			

Abbreviations: CI, confidence interval; FAS, full analysis set; hsCRP, high-sensitivity c-reactive protein; LS, least squares; MMRM, mixed-effect model repeated measures; n, number of patients with measurements at both baseline and the post-baseline visit; N, number of patients in the randomised treatment group; N/A, not applicable; SE, standard error.

B.2.6.10 Secondary endpoint: BASFI change from baseline in all patients

LS mean BASFI change from baseline was statistically significantly greater in the secukinumab 150 mg Load and No Load groups compared with placebo (−1.75 and −1.64 vs −1.01) (Table 22).

Table 22: Secondary endpoint: BASFI change from baseline in all patients using MMRM, Week 16, FAS

Treatment group	n	Within treatment	Treatment contrast			
		LS mean change (SE)	Comparison	LS mean (SE)	95% CI	p-value
Secukinumab 150 mg Load (N=185)	181	–1.75 (0.202)	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	177	–1.64 (0.204)	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	177	–1.01 (0.206)	N/A			

Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index; CI, confidence interval; FAS, full analysis set; LS, least squares; M, number of patients in the treatment group of the specified analysis set; MMRM, mixed-effect model repeated measures; n, number of patients with measures at both baseline and the corresponding post baseline visit; N, number of patients in each treatment group of the specified analysis; N/A, not applicable; SE, standard error.

B.2.6.11 Secondary endpoint: MRI SI joint oedema score change from baseline in all patients

At Week 16, the mean SI joint oedema score change from baseline using analysis of covariance (ANCOVA) based on multiple imputation was statistically significantly greater for secukinumab 150 mg Load and No Load compared with placebo (−1.68 and −1.03 vs −0.39) (Table 23).

Table 23: Secondary endpoint: MRI SI joint oedema score change from baseline in all patients using ANCOVA based on multiple imputation, Week 16, FAS

Treatment group	n	Mean (SE)	Comparison	Estimate	SE	p-value
Secukinumab 150 mg Load (N=185)	180	–1.68 (0.24)	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	177	–1.03 (0.18)	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	174	–0.39 (0.15)	N/A			

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; MRI, magnetic resonance imaging; n, number of patients with measures at both baseline and the corresponding post baseline visit; N, number of patients in each treatment group of the specified analysis set; N/A, not applicable; OR, odds ratio; SE, standard error; SI sacroiliac.

B.2.6.12 Secondary endpoint: ASAS20 response in all patients

ASAS20 response in all patients using non-responder imputation at Week 16 was [redacted] in the secukinumab 150 mg Load and No Load groups compared with the placebo group ([redacted] and [redacted] vs [redacted]) (Table 24).

Table 24: Secondary endpoint: ASAS20 response in all patients using non-responder imputation, Week 16, FAS

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=185)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	0.0260
Secukinumab 150 mg No Load (N=184)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	N/A			

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; OR, odds ratio.

B.2.6.13 Secondary endpoint: SF-36 change from baseline in all patients

LS mean short-form-36 (SF-36) physical component summary (PCS) change from baseline was statistically significantly greater in the secukinumab 150 mg Load and No Load groups compared with placebo (5.71 and 5.57 vs 2.93) (Table 25).

Table 25: Secondary endpoint: SF-36 PCS change from baseline in all patients using MMRM, Week 16, FAS

Treatment group	n	Within treatment	Treatment contrast			
		LS mean change (SE)	Comparison	LS mean (SE)	95% CI	p-value
Secukinumab 150 mg Load (N=185)	182	5.71 (0.683)	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	176	5.57 (0.694)	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	178	2.93 (0.705)	N/A			

Abbreviations: CI, confidence interval; FAS, full analysis set; hsCRP, high-sensitivity c-reactive protein; LS, least squares; MMRM, mixed-effect model repeated measures; n, number of patients with measures at both baseline and the corresponding post baseline visit; N, number of patients in each treatment group of the specified analysis set; N/A, not applicable; PCS, physical component summary; SE, standard error; SF-36, short form-36.

As seen for the SF-36 PCS, LS mean change from baseline in SF-36 mental component summary (MCS) was [redacted] for both secukinumab groups than placebo ([redacted] and [redacted] vs [redacted]) (Table 26).

Table 26: Secondary endpoint: SF-36 MCS change from baseline in all patients using MMRM, Week 16, FAS

Treatment group	n	Within treatment	Treatment contrast			
		LS mean change (SE)	Comparison	LS mean (SE)	95% CI	p-value
Secukinumab 150 mg Load (N=185)	182	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	176	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	178	[redacted]	N/A			

Abbreviations: CI, confidence interval; FAS, full analysis set; hsCRP, high-sensitivity c-reactive protein; LS, least squares; MCS, mental component summary; MMRM, mixed-effect model repeated measures; n, number of subjects with measures at both baseline and the corresponding post baseline visit; N, number of subjects in each treatment group of the specified analysis set; N/A, not applicable; SE, standard error; SF-36, short form-36.

B.2.6.14 Secondary endpoint: ASQoL change from baseline in all patients

LS mean Ankylosing Spondylitis Quality of Life (ASQoL) change from baseline was statistically significantly greater in the secukinumab 150 mg Load and No Load groups compared with placebo (−3.45 and −3.62 vs −1.84) (Table 27).

Table 27: Secondary endpoint: ASQoL change from baseline in all patients using MMRM, Week 16, FAS

Treatment group	n	Within treatment	Treatment contrast			
		LS mean change (SE)	Comparison	LS mean (SE)	95% CI	p-value
Secukinumab 150 mg Load (N=185)	181	–3.45 (0.408)	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	176	–3.62 (0.414)	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	177	–1.84 (0.421)	N/A			

Abbreviations: ASQoL, Ankylosing Spondylitis Quality of Life; CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed-effect model repeated measures; n, number of subjects with measures at both baseline and the corresponding post baseline visit; N, number of subjects in each treatment group of the specified analysis set; N/A, not applicable; SE, standard error.

B.2.6.15 Secondary endpoint: ASAS partial remission in all patients

ASAS partial remission in all patients using non-responder imputation at Week 16 was achieved by a statistically significantly higher proportion of patients in the secukinumab 150 mg Load and No Load groups compared with the placebo group (21.6% and 21.2% vs 7.0%) (Table 28).

Table 28: Secondary endpoint: ASAS partial remission in all patients using non-responder imputation, Week 16, FAS

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=185)	40/185 (21.6)	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	39/184 (21.2)	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	13/186 (7.0)	N/A			

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; OR, odds ratio.

B.2.6.16 Health-related quality of life

B.2.6.16.1 *SF-36 change from baseline at Week 16*

The change from baseline in SF-36 PCS at Week 16 was assessed as a secondary endpoint. Results are summarised in Section B.2.6.13.

B.2.6.16.2 *SF-36 PCS and MCS response at Week 16*

MCS and PCS responders were defined as patients with an improvement of ≥ 2.5 points. SF-36 MCS and PCS response using non-responder imputation up to Week 16 is summarised in Table 29 and Table 30.

Table 29: MCS response in all patients using non-responder imputation, Week 16, FAS

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=185)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	N/A			

Abbreviations: CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; MCS, Mental component summary score; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; OR, odds ratio.

Table 30: PCS response in all patients using non-responder imputation, Week 16, FAS

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=185)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	N/A			

Abbreviations: CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; OR, odds ratio; PCS, Physical component summary score.

B.2.6.16.3 *ASQoL at Week 16*

The change from baseline in ASQoL at Week 16 was assessed as a secondary endpoint. Results are summarised in Section B.2.6.14.

B.2.6.16.4 *FACIT-Fatigue at Week 16*

FACIT-Fatigue change from baseline using MMRM at Week 16 is presented in Table 31.

Table 31: FACIT change from baseline in all patients using MMRM, Week 16, FAS

	Within treatment		Treatment contrast in LS mean (Change)				
Treatment group	**LS Mean Change**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]	N/A				

Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed-effect model repeated measures; N, number of patients in the randomised treatment group; N/A, not applicable; SE, standard error.

B.2.6.16.5 *EQ-5D at Week 16*

EuroQol-5 dimensions (EQ-5D) health state assessment change from baseline using MMRM at Week 16 is presented in Table 32.

Table 32: EQ5D health state assessment change from baseline in all patients using MMRM, Week 16, FAS

	Within treatment		Treatment contrast in LS mean (Change)				
Treatment group	**LS Mean Change**	**SE**	**Comparison**	**LS Mean**	**SE**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]	N/A				

Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed-effect model repeated measures; N, number of patients in the randomised treatment group; N/A, not applicable; SE, standard error.

B.2.6.16.6 *WPAI-GH at Week 16*

The mean change of Work Productivity and Activity Impairment Questionnaire – General Health (WPAI-GH) domains from baseline using observed data is summarised in Table 33.

Table 33: Summary of WPAI-GH change from baseline in all patients using observed data, Week 16, FAS

Original treatment	Current treatment	n	Mean	SD
Percent work time missed due to health				
Secukinumab 150 mg Load (N=185)	Secukinumab 150 mg Load	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	Secukinumab 150 mg No Load	[redacted]	[redacted]	[redacted]
Placebo (N=186)	Placebo	[redacted]	[redacted]	[redacted]
Percent impairment while working due to health				
Secukinumab 150 mg Load (N=185)	Secukinumab 150 mg Load	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	Secukinumab 150 mg No Load	[redacted]	[redacted]	[redacted]
Placebo (N=186)	Placebo	[redacted]	[redacted]	[redacted]
Overall work impairment due to health				
Secukinumab 150 mg Load (N=185)	Secukinumab 150 mg Load	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	Secukinumab 150 mg No Load	[redacted]	[redacted]	[redacted]
Placebo (N=186)	Placebo	[redacted]	[redacted]	[redacted]
Percent activity impairment due to health				
Secukinumab 150 mg Load (N=185)	Secukinumab 150 mg Load	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	Secukinumab 150 mg No Load	[redacted]	[redacted]	[redacted]
Placebo (N=186)	Placebo	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; FAS, full analysis set; n, number of subjects with measures at both baseline and the corresponding post baseline visit; N, number of subjects in each treatment group of the specified analysis set; N/A, not applicable; SD, standard deviation; WPAI-GH, Work Productivity and Activity Impairment - General Health.

B.2.6.17 Exploratory analyses

An overview of 16-week exploratory analyses is provided in Table 34.

Table 34: Summary of exploratory analyses, Week 16, FAS

BASMI linear change from baseline in all patients using MMRM						
Treatment group	**n**	**Within treatment**	**Treatment contrast**			
		LS mean change (SE)	**Comparison**	**LS mean (SE)**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	179	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	174	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	175	[redacted]	N/A			
MASES change from baseline in all patients using MMRM						
Treatment group	**n**	**Within treatment**	**Treatment contrast**			
		LS mean change (SE)	**Comparison**	**LS mean change (SE)**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	182	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	176	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	179	[redacted]	N/A			
ASDAS-CRP change from baseline in all patients using MMRM						
Treatment group	**n**	**Within treatment**	**Treatment contrast**			
		LS mean change (SE)	**Comparison**	**LS mean change (SE)**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	175	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	175	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	175	[redacted]	N/A			

ASDAS-ESR change from baseline in all patients using MMRM						
Treatment group	**n**	**Within treatment**	**Treatment contrast**			
		LS mean change (SE)	**Comparison**	**LS mean change (SE)**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	174	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	176	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	176	[redacted]	N/A			

ASDAS-CRP clinically important improvement in all patients using non-responder imputation					
Treatment group	**n/M (%)**	**Comparison**	**OR**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	N/A			

ASDAS-ESR clinically important improvement in all patients using non-responder imputation					
Treatment group	**n/M (%)**	**Comparison**	**OR**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	N/A			

ASDAS-CRP major improvement in all patients using non-responder imputation					
Treatment group	**n/M (%)**	**Comparison**	**OR**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	N/A			

ASDAS-ESR major improvement in all patients using non-responder imputation					
Treatment group	**n/M (%)**	**Comparison**	**OR**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	N/A			

ASDAS-CRP inactive disease in all patients using non-responder imputation					
Treatment group	**n/M (%)**	**Comparison**	**OR**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	N/A			
ASDAS-ESR inactive disease in all patients using non-responder imputation					
Treatment group	**n/M (%)**	**Comparison**	**OR**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	[redacted]	N/A			

Adjusted swollen and tender 44 joint count change from baseline in all patients using non-responder imputation						
Treatment group	**n**	**Within treatment**	**Treatment contrast**			
		LS mean change (SE)	**Comparison**	**LS mean change (SE)**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	64	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	75	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	66	[redacted]	N/A			

Inflammation represented by duration and severity of morning stiffness (mean of BASDAI questions 5 and 6) in all patients using MMRM						
Treatment group	**n**	**Within treatment**	**Treatment contrast**			
		LS mean change (SE)	**Comparison**	**LS mean change (SE)**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	181	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	177	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	177	[redacted]	N/A			

Patient's global assessment of disease activity in all patients using MMRM						
Treatment group	**n**	**Within treatment**	**Treatment contrast**			
		LS mean change (SE)	**Comparison**	**LS mean change (SE)**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	176	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	176	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	177	[redacted]	N/A			
Back pain in all patients using MMRM						
Treatment group	**n**	**Within treatment**	**Treatment contrast**			
		LS mean change (SE)	**Comparison**	**LS mean change (SE)**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=185)	180	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	177	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	177	[redacted]	N/A			
Change in ASspiMRI-a in all patients using multiple imputation						
Treatment group	**n**	**Within treatment**	**Treatment contrast**			
		Mean change (SE)	**Comparison**	**Mean change (SE)**	**95% CI**	
Secukinumab 150 mg Load (N=185)	179	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
			vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	177	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=186)	176	[redacted]	N/A			
Change in ESR in all patients						
Treatment group	**n**	**Mean change**	**Treatment contrast**			
Secukinumab 150 mg Load (N=185)	179	[redacted]	NR			
Secukinumab 150 mg No Load (N=184)	177	[redacted]	NR			
Placebo (N=186)	176	[redacted]	NR			

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASspiMRI-a, Ankylosing spondylitis spine MRI score for activity; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI,

confidence interval; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; FAS, full analysis set; LS, least squares; M, number of patients in the treatment group of the specified analysis set; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; n, number of subjects with measures at both baseline and the corresponding post baseline visit; N, number of subjects in each treatment group of the specified analysis set; N/A, not applicable; NR, not reported; OR, odds ratio; SE, standard error.

B.2.6.18 Summary of hierarchical testing, Week 52 (Analysis Plan B)

The 16-week data already presented in previous sections is the primary information for this submission. These interim 52-week analyses are submitted as longer-term supporting evidence

In this interim analysis of the Week 52 hypothesis testing, [redacted]. [redacted] (Table 35).

Table 35: Overview of hierarchical testing, Week 52, FAS/FAS2

Hypothesis number	Endpoint	Comparison vs placebo	Info fraction	Unadjusted p-value	Adjusted p-value		Statistically significant
					Group sequential	Testing hierarchy	
1	ASAS40 in TNFα-naïve patients at Week 52	Secukinumab 150 mg No Load	[redacted]	[redacted]	[redacted]	[redacted]	Yes
2	ASAS40 at Week 52		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	ASAS40 at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	ASAS40 in TNFα-naïve patients at Week 52	Secukinumab 150 mg Load	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	ASAS40 at Week 52		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	ASAS40 at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	BASDAI at Week 16	Secukinumab 150 mg No Load	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	BASDAI50 at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	BASDAI50 at Week 52		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	hsCRP at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	SF-36 PCS at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	ASQoL at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	ASAS 5/6 at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	ASAS20 at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	BASFI at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	SI joint oedema on MRI at Week 16		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	ASDAS-CRP inactive disease at Week 52		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; hsCRP, high sensitivity c-reactive protein, MRI, magnetic resonance imaging; SF-36, Short Form-36; SI, sacroiliac; TNFα, tumour necrosis factor alpha.

B.2.6.19 Primary endpoint: ASAS40 response in TNFα-naïve patients (Analysis Plan B)

The primary efficacy variable of the study was met: secukinumab 150 mg No Load was [redacted] vs placebo for ASAS40 response in TNFα-naïve patients at Week 52 using non-responder imputation ([redacted] vs [redacted]; [redacted]) (Table 36). Secukinumab 150 mg Load also had a [redacted] ASAS40 response than placebo ([redacted] vs [redacted]; [redacted]).

Table 36: Primary endpoint: ASAS40 response in TNFα-naïve patients using non-responder imputation, Week 52, FAS2

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=114)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=115)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=119)	[redacted]	N/A			

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS2, full analysis set 2; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; OR, odds ratio; TNFα, tumour necrosis factor alpha.

The time course of ASAS40 response in TNFα-naïve patients is shown in Figure 9.

Figure 9: ASAS40 response in TNFα-naïve patients with 95% CI using non-responder imputation, Week 52, FAS2

★ unadjusted p-value ≤0.05.
Abbreviations: TNFα, tumour necrosis factor alpha

Sensitivity analyses support the primary analysis of the primary endpoint (Table 37).

Table 37: Sensitivity analyses: ASAS40 response in TNFα-naïve patients, Week 52, FAS2

Treatment group	Current treatment	n/M (%)	Comparison	OR	95% CI	p-value
Observed data						
Secukinumab 150 mg Load (N=114)	Secukinumab 150 mg Load	[redacted]	N/A	NR	[redacted]	NR
	Open label secukinumab 150 mg	[redacted]			[redacted]	
	SoC	[redacted]			[redacted]	
	Total	[redacted]			[redacted]	
Secukinumab 150 mg No Load (N=115)	Secukinumab 150 mg No Load	[redacted]	N/A	NR	[redacted]	NR
	Open label secukinumab 150 mg	[redacted]			[redacted]	
	Total	[redacted]			[redacted]	
Placebo (N=119)	Placebo	[redacted]	N/A	NR	[redacted]	NR
	Open label secukinumab 150 mg	[redacted]			[redacted]	
	Total	[redacted]			[redacted]	
Modified rescue penalty						
Secukinumab 150 mg Load (N=114)	N/A	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=115)		[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=119)		[redacted]	vs placebo	[redacted]	[redacted]	[redacted]

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS2, full analysis set 2; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; NR, not reported; OR, odds ratio; SoC, standard-of-care; TNFα, tumour necrosis factor alpha.

B.2.6.20 Secondary endpoints, 52 weeks (Analysis Plan B)

An overview of secondary endpoint results (not already presented in Sections B.2.6.4 to B.2.6.15 as part of the 16-week analysis) from the interim 52-week analysis is provided in Table 38.

Table 38: Summary of secondary endpoint results, Week 52, FAS2

ASAS40 response in all patients using non-responder imputation					
Treatment group	**n/M (%)**	**Comparison**	**OR**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=133)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=132)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=132)	[redacted]	N/A			
BASDAI50 response in all patients using non-responder imputation					
Treatment group	**n/M (%)**	**Comparison**	**OR**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=133)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=132)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=132)	[redacted]	N/A			
ASDAS-CRP inactive disease in all patients using non-responder imputation					
Treatment group	**n/M (%)**	**Comparison**	**OR**	**95% CI**	**p-value**
Secukinumab 150 mg Load (N=133)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=132)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=132)	[redacted]	N/A			
ASQoL change from baseline in all patients using RANK based analysis					
Treatment group	**n/M (%)†**	**Comparison**	**Mean**	**SD**	**p-value**
Secukinumab 150 mg Load (N=133)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=132)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=132)	[redacted]	N/A	[redacted]	[redacted]	[redacted]

†Patients with no intercurrent event only
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CI, confidence interval; CRP, c-reactive protein; FAS2, full analysis set 2; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; OR, odds ratio; SD, standard deviation.

B.2.7 Subgroup analysis

A summary of the subgroup results is provided in Appendix E. Pre-planned subgroup analyses were conducted according to randomisation strata:

- Objective signs of inflammation (CRP+ and MRI+; CRP+ and MRI–; CRP– and MRI+)
- Previous biological treatment experience (TNFα-naïve; TNF-IR).

B.2.7.1 According to objective signs of inflammation

B.2.7.1.1 *ASAS40 response*

The subgroup analyses showed that ASAS40 response was [redacted] in the secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) groups than the placebo group ([redacted]) for TNFα-naïve patients who were CRP+ and MRI+ at screening (Table 39). In the two other randomisation strata (CRP+ and MRI–; CRP– and MRI+) ASAS40 response in TNFα-naïve patients showed [redacted] in the secukinumab 150 mg Load and No Load groups over time compared with placebo.

Table 39: Subgroup analyses: ASAS40 response in TNFα-naïve patients, FAS

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
CRP+ and MRI+					
Secukinumab 150 mg Load (N=49)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=52)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=50)	[redacted]	N/A			
CRP+ and MRI–					
Secukinumab 150 mg Load (N=45)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=44)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=45)	[redacted]	N/A			
CRP– and MRI+					
Secukinumab 150 mg Load (N=70)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=70)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=76)	[redacted]	N/A			

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; CRP, c-reactive protein; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; MRI, magnetic resonance imagining; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; NR, not reported; OR, odds ratio; TNFα, tumour necrosis factor alpha.

Similar results were observed in the whole trial population (Table 40).

Table 40: Subgroup analyses: ASAS40 response in all patients, FAS

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
CRP+ and MRI+					
Secukinumab 150 mg Load (N=54)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=57)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (N=55)	[redacted]	N/A			
CRP+ and MRI–					
Secukinumab 150 mg Load (N=52)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=51)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=51)	[redacted]	N/A			
CRP– and MRI+					
Secukinumab 150 mg Load (N=79)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=76)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=80)	[redacted]	N/A			

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; CRP, c-reactive protein; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; MRI, magnetic resonance imagining; n, number of patients responded; N, number of patients in the randomised treatment group; N/A, not applicable; NR, not reported; OR, odds ratio.

B.2.7.1.2 *ASAS 5/6 response*

For patients who were CRP+ and MRI+ at Screening, ASAS 5/6 response at Week 16 using non-responder imputation was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. For patients who were CRP+ and MRI– at screening, ASAS 5/6 response was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively. For patients who were CRP– and MRI+ at screening, ASAS 5/6 response was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.1.3 *BASDAI change from baseline*

For patients who were CRP+ and MRI+ at screening, the LS mean BASDAI change from baseline at Week 16 using MMRM was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), both secukinumab arms [redacted] vs placebo. For patients who were CRP+ and MRI– at screening, LS mean BASDAI change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively. For patients who were CRP– and MRI+ at screening, LS mean BASDAI change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.1.4 *BASDAI50 response*

For patients who were CRP+ and MRI+ at screening, BASDAI50 response using non-responder imputation at Week 16 was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), both secukinumab arms [redacted] vs placebo. For patients who were CRP+ and MRI– at screening, BASDAI50 response was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively. For patients who were CRP– and MRI+ at screening, BASDAI50 response was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.1.5 *BASFI change from baseline*

For patients who were CRP+ and MRI+ at screening, BASFI change from baseline using MMRM at Week 16 was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. For patients who were CRP+ and MRI– at screening, BASFI change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively. For patients who were CRP– and MRI+ at screening, BASFI change from baseline was [redacted] with secukinumab 150

mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.1.6 *ASAS20 response*

For patients who were CRP+ and MRI+ at screening, ASAS20 response at Week 16 using non-responder imputation was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] and [redacted] vs placebo, respectively. For patients who were CRP+ and MRI– at screening, ASAS20 response was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively. For patients who were CRP– and MRI+ at screening, ASAS20 response was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.1.7 *SF-36 change from baseline*

For patients who were CRP+ and MRI+ at screening, the SF-36 PCS LS mean change from baseline using MMRM at Week 16 was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. For patients who were CRP+ and MRI– at screening, SF-36 PCS LS mean change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively. For patients who were CRP– and MRI+ at screening, SF-36 PCS LS mean change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively.

Similarly, the LS mean change from baseline in SF-36 MCS using MMRM at Week 16 was also [redacted] in both secukinumab groups than in the placebo group ([redacted] for secukinumab 150 mg Load and [redacted] for secukinumab 150 mg No Load vs [redacted] for placebo), [redacted] vs placebo, respectively. For patients who were CRP+ and MRI– at screening, LS mean change from baseline in SF-36 MCS was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively. For patients who were CRP– and MRI+ at screening, LS mean change from baseline in SF-36

MCS was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.1.8 *ASQoL change from baseline*

For patients who were CRP+ and MRI+ at screening, the LS mean ASQoL change from baseline using MMRM at Week 16 was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. For patients who were CRP+ and MRI– at screening, LS mean ASQoL change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively. For patients who were CRP– and MRI+ at screening, LS mean ASQoL change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load, and [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.1.9 *ASAS partial remission*

For patients who were CRP+ and MRI+ at screening, ASAS partial remission at Week 16 using non-responder imputation was higher with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. For patients who were CRP+ and MRI– at screening, ASAS partial remission was [redacted] for secukinumab 150 mg Load, [redacted] for secukinumab 150 mg No Load, and [redacted] for placebo, [redacted] vs placebo, respectively. For patients who were CRP– and MRI+ at screening, LS mean BASDAI change from baseline was [redacted] for secukinumab 150 mg Load, [redacted] for secukinumab 150 mg No Load, and [redacted] for placebo, [redacted] vs placebo, respectively.

B.2.7.2 According to previous biological treatment experience

B.2.7.2.1 *ASAS40 response*

The subgroup analyses showed that in TNFα-naïve patients, ASAS40 response was [redacted] in the secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) groups than the placebo group ([redacted]) (Table 41). In TNF-IR patients, ASAS40 response showed a

[redacted] higher response rates in the secukinumab 150 mg Load and No Load groups compared with placebo.

Table 41: Subgroup analyses: ASAS40 response, FAS

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
TNFα-naïve patients					
Secukinumab 150 mg Load (N=164)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=166)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=171)	[redacted]	N/A			
TNF-IR patients					
Secukinumab 150 mg Load (N=21)	[redacted]	vs No Load	[redacted]	[redacted]	[redacted]
		vs placebo	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=18)	[redacted]	vs placebo	[redacted]	[redacted]	[redacted]
Placebo (N=15)	[redacted]	N/A			

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N/A, not applicable; NR, not reported; OR, odds ratio; TNFα, tumour necrosis factor alpha; TNF-IR, tumour necrosis factor – inadequate response.

B.2.7.2.2 *ASAS 5/6 response*

For TNFα-naïve patients, ASAS 5/6 response at Week 16 using non-responder imputation was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. In TNF-IR patients, ASAS 5/6 response was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load vs [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.2.3 *BASDAI change from baseline*

For TNFα-naïve patients, the LS mean BASDAI change from baseline at Week 16 using MMRM was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. In TNF-IR patients, LS mean BASDAI change from baseline was [redacted] with secukinumab 150 mg Load, [redacted]

with secukinumab 150 mg No Load vs [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.2.4 ***BASDAI50 response***

For TNFα-naïve patients, BASDAI50 response using non-responder imputation at Week 16 was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), both secukinumab arms [redacted] vs placebo. In TNF-IR patients, BASDAI50 response was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load vs [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.2.5 ***hsCRP change from baseline***

For TNFα-naïve patients, hsCRP change from baseline using MMRM at Week 16 was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. In TNF-IR patients, hsCRP change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load vs [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.2.6 ***BASFI change from baseline***

For TNFα-naïve patients, BASFI change from baseline using MMRM at Week 16 was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. In TNF-IR patients, BASFI change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load vs [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.2.7 ***MRI SI joint oedema score change from baseline***

For TNFα-naïve patients, MRI SI joint oedema score change from baseline using ANCOVA at Week 16 was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), both secukinumab arms [redacted] vs placebo. In TNF-IR

patients, MRI SI joint oedema score change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load vs [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.2.8 *ASAS20 response*

For TNFα-naïve patients, ASAS20 response at Week 16 using non-responder imputation was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. In TNF-IR patients, ASAS20 response was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load vs [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.2.9 *SF-36 change from baseline*

For TNFα-naïve patients, the SF-36 PCS LS mean change from baseline using MMRM at Week 16 was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. In TNF-IR patients, SF-36 PCS LS mean change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load vs [redacted] with placebo, [redacted] vs placebo, respectively.

Similarly, the LS mean change from baseline in SF-36 MCS using MMRM at Week 16 was also [redacted] in both secukinumab groups than in the placebo group ([redacted] for secukinumab 150 mg Load and [redacted] for secukinumab 150 mg No Load vs [redacted] for placebo), [redacted] vs placebo, respectively. In TNF-IR patients, SF-36 MCS LS mean change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load vs [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.2.10 *ASQoL change from baseline*

For TNFα-naïve patients, the LS mean ASQoL change from baseline using MMRM at Week 16 was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), [redacted] vs placebo, respectively. In TNF-IR patients, LS mean

ASQoL change from baseline was [redacted] with secukinumab 150 mg Load, [redacted] with secukinumab 150 mg No Load vs [redacted] with placebo, [redacted] vs placebo, respectively.

B.2.7.2.11 *ASAS partial remission*

For TNFα-naïve patients, ASAS partial remission at Week 16 using non-responder imputation was [redacted] with secukinumab 150 mg Load ([redacted]) and secukinumab 150 mg No Load ([redacted]) than with placebo ([redacted]), both secukinumab arms [redacted] vs placebo.

[redacted].

B.2.8 Meta-analysis

A pairwise meta-analysis was not carried out as there is only one trial of secukinumab in nr-axSpA. An NMA (network meta-analysis) was conducted to estimate the relative efficacy of secukinumab and comparators (Section B.2.9).

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Overview

An SLR was conducted to identify clinical evidence relating to biologic agents in the treatment of non-radiographic axial spondyloarthritis (nr-axSpA; Appendix D) (60). No direct evidence comparing secukinumab with the comparators defined in the final scope was identified. Therefore, an NMA was performed in order to assess the relative efficacy and safety of secukinumab compared with these approved biologic treatments (70).

The primary objective of the NMA was to estimate the relative efficacy of secukinumab, etanercept, adalimumab, golimumab, and certolizumab pegol for the treatment of non-radiographic nr-axSpA based on currently available RCT evidence. The main outcomes of interest were ASAS40 and BASDAI50 response criteria, as well as changes from baseline in BASDAI and BASFI scores.

In addition to RCTs identified in the SLR, the unpublished PREVENT trial was also included. Two studies identified in the SLR were excluded from the NMA:

- ABILITY-3 (adalimumab) was excluded as it was a withdrawal study with no relevant data available at 12–16 weeks post-treatment exposure.
- ESTHER (etanercept) was excluded from the analysis as it was not a placebo-controlled trial (sulfasalazine as comparator), which meant it did not connect to the evidence network.

Following exclusion of the above studies, a total of seven RCTs comprising approximately 1,359 patients were included in the analysis. All trials compared active treatments with placebo. The evidence base was restricted to TNFα-naïve patients who showed objective signs of inflammation to align with the final scope (Table 1). Both 12- and 16-week time points were included, as data for comparators were only available at either 12 or 16 weeks. Both 12- and 16-week data were available for secukinumab. 16-week secukinumab data were used in the NMA base-case (as this was the primary endpoint for PREVENT Analysis Plan A), with 12-week data used in a sensitivity analysis.

Several NMA analyses were conducted based on different assumptions e.g. independence of treatment effects, exchangeability, fixed vs random effects, and joint modelling of correlated parameters. Additionally, meta-regression analysis was conducted to explore heterogeneity.

B.2.9.2 Summary of included trials

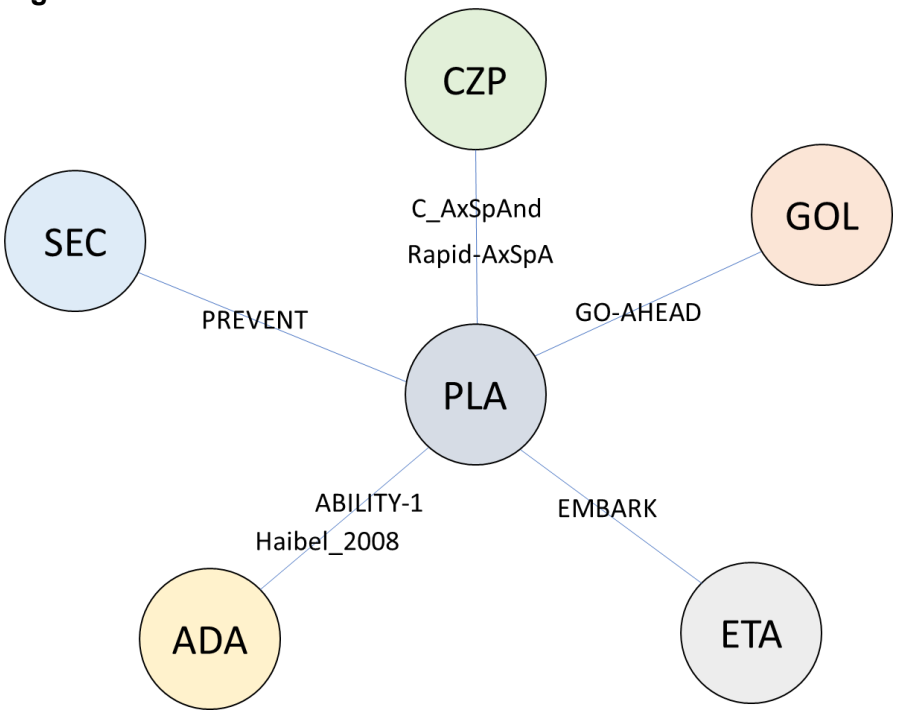
Studies included in the NMA are summarised in Table 42.

Table 42: Summary of the trials used to carry out the indirect or mixed treatment comparison

Trial (reference)	Adalimumab	Certolizumab pegol 200 mg	Certolizumab pegol 400 mg	Etanercept	Golimumab	Secukinumab	Placebo
ABILITY-1 (51, 71)	✓						✓
Haibel_2008 (47)	✓						✓
C-AxSpAnd (45)		✓					✓
RAPID-AxSpA (49, 72, 73)		✓	✓				✓
EMBARK (46)				✓			✓
GO-AHEAD (50)					✓		✓
PREVENT (unpublished)						✓	✓

The network diagram is presented in Figure 10. Note that this is the non-outcome specific network presenting the maximum amount of evidence; not all studies report every outcome.

Figure 10: Overall network



Vertices denote treatments and edges denote the evidence connections between treatments, with trial names superimposed.
Abbreviations: ADA, adalimumab; CZP, certolizumab pegol; ETA, etanercept; GOL, golimumab; PLA, placebo; SEC, secukinumab.

B.2.9.3 Methodology

Full details of NMA methodology are presented in Appendix D. A number of NMA analyses were conducted based on different assumptions such as independence of treatment effects, exchangeability, fixed vs random effects, joint modelling of correlated parameters. Additionally, placebo response-adjusted models were explored due to heterogeneity in placebo response between studies.

The base case network meta-analysis used in the cost-effectiveness modelling was based on a joint modelling approach to relate BASDAI50 to BASDAI change from baseline, alongside correlations between BASDAI change from baseline and BASFI baseline, as preferred by the York ERG in TA383 (16).

An overview of the analyses is provided in Table 43.

Table 43: Base case and sensitivity analyses

	Base case	Sensitivity analysis
Time-point	Comparators: 12–16 weeks (pooled) Secukinumab: 16 weeks	Comparators: As per base case Secukinumab: 12 weeks
Treatment effect type	Fixed effects Exchangeable effects	Random effects with non-informative and informative priors
Studies	All studies present as per Figure 10	Haibel 2008 excluded

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Disease Functional Index; TNFα, tumour necrosis factor alpha.

Assumptions underpinning the NMAs (such as correlations between endpoints) were informed by discussions with clinical experts (74).

B.2.9.4 Exploratory analyses

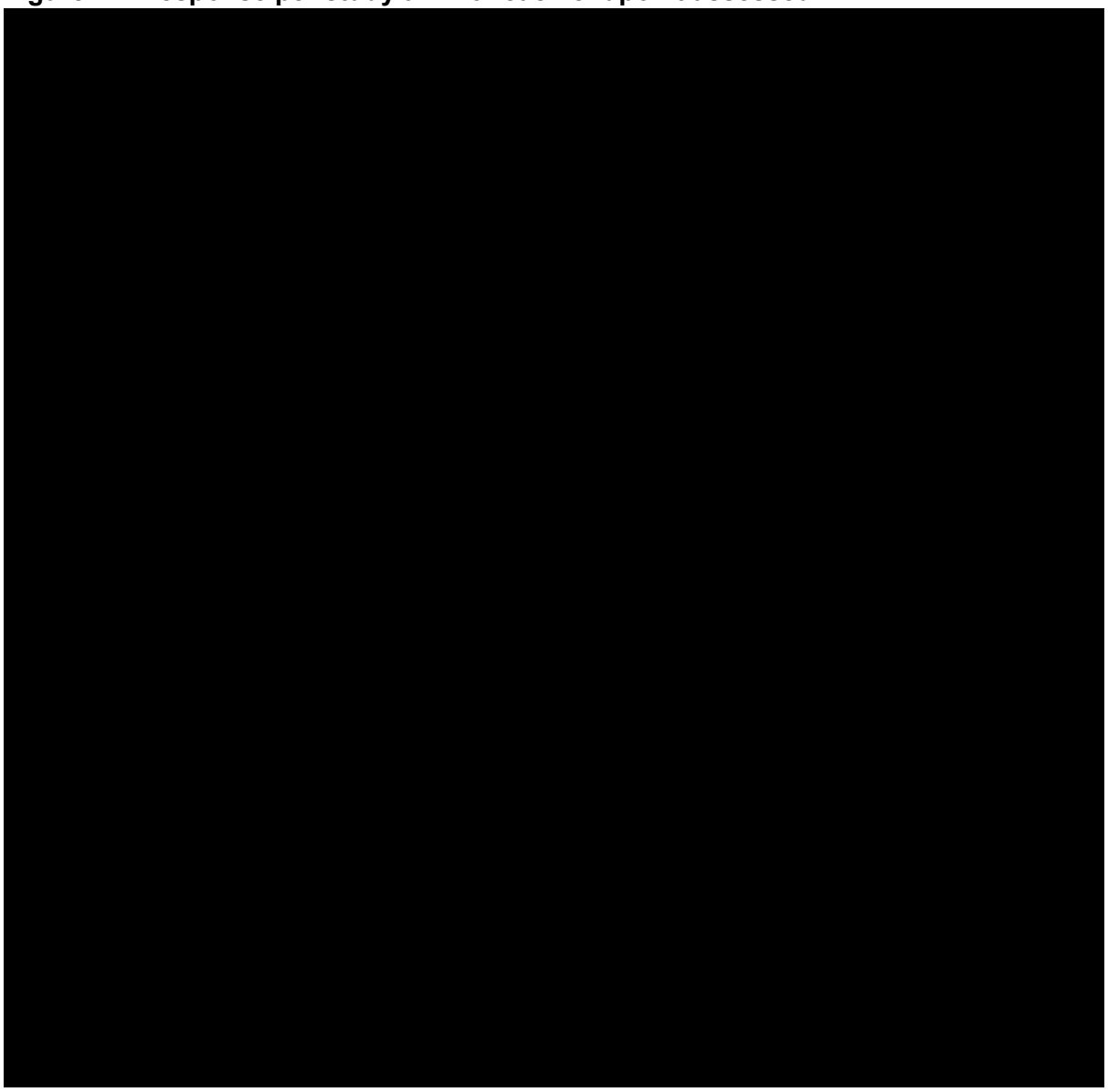
B.2.9.4.1 *Feasibility assessment*

A feasibility assessment was conducted to evaluate the similarity of studies for pooling in an NMA. This is described in detail in Appendix D.

B.2.9.4.2 *Assessment of baseline response rates*

[redacted]

Figure 11: Response per study/arm for each endpoint assessed



B.2.9.4.3 ***Heterogeneity and meta-regression***

[redacted]

B.2.9.5 Results

B.2.9.5.1 *Principal analysis*

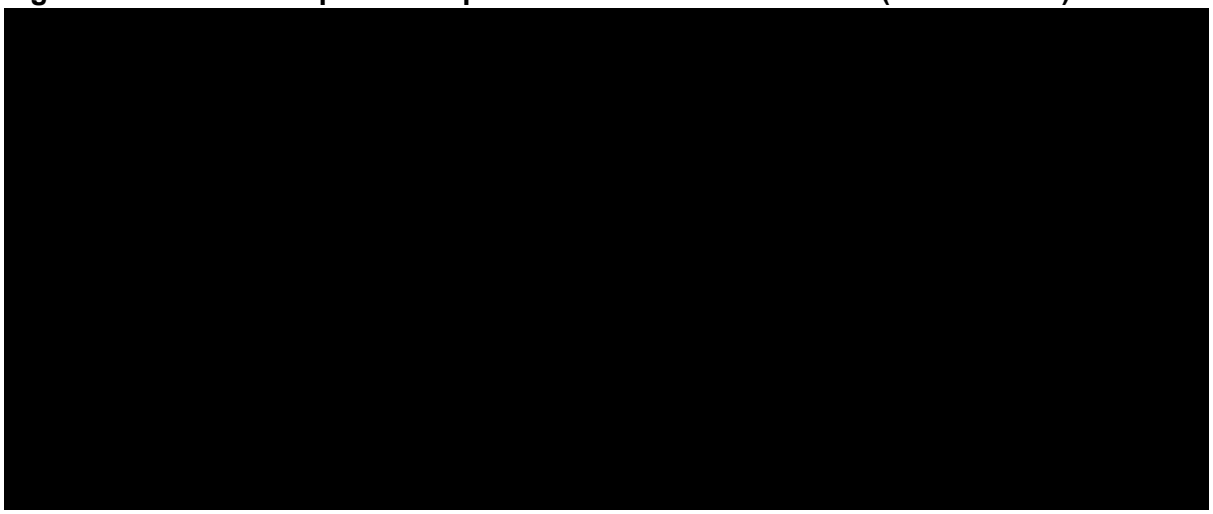
Uncorrelated/independent outcomes

[redacted]

ASAS40 response – fixed effects

Figure 12

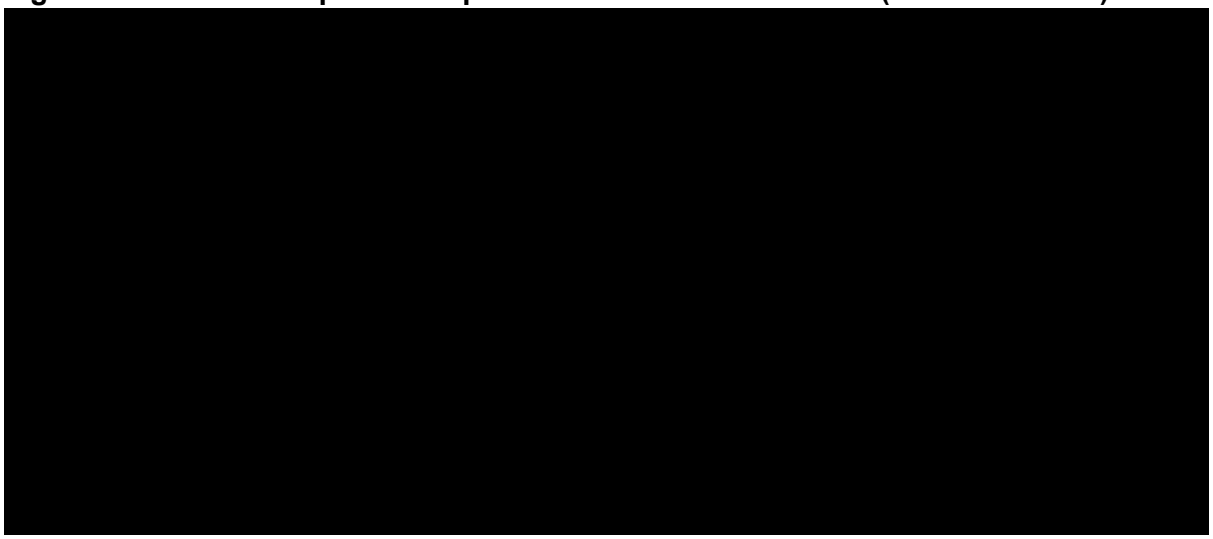
Figure 12: ASAS40 responses expressed as mean relative risk (fixed effects)



ASAS40 response – random effects

13

Figure 13: ASAS40 responses expressed as mean relative risk (random effects)



ASAS40 response – model fit results

Table 44

Table 44: Model comparison for ASAS40 response

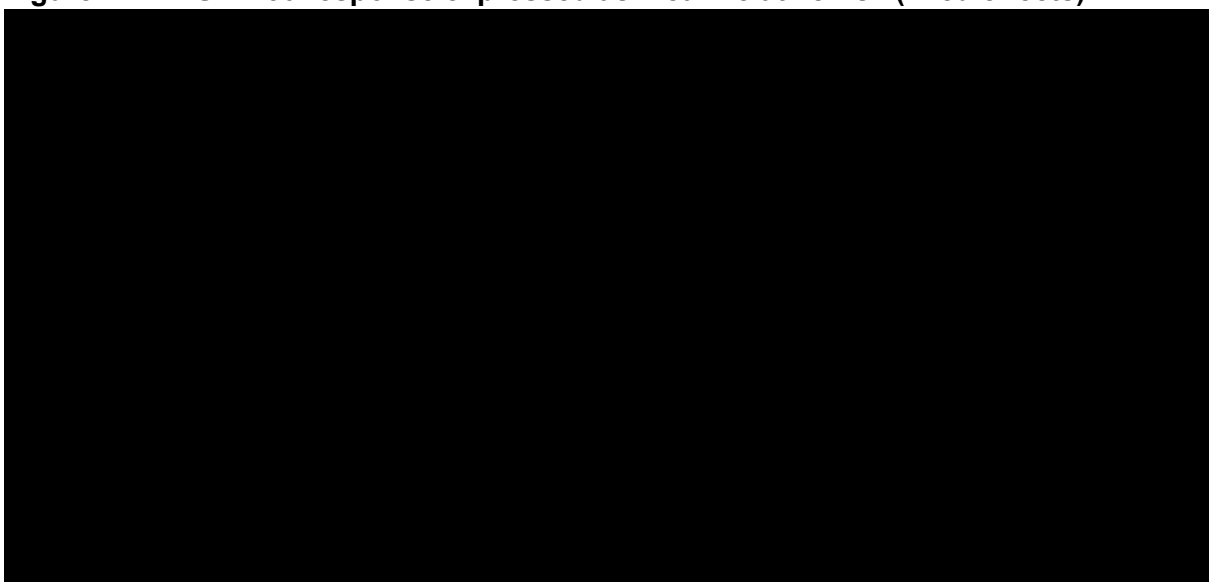
[redacted]

BASDAI50 response – fixed effects

Figure 14 [redacted]

[redacted]

Figure 14: BASDAI50 response expressed as mean relative risk (fixed effects)



BASDAI50 response – random effects

[redacted]

15 [redacted]

Figure 15: BASDAI50 response expressed as mean relative risk (random effects)

[redacted]

BASDAI50 response – model fit results

[redacted]

Table 45 [redacted]

Table 45: Model comparison for various types of models for BASDAI50 response

[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

[redacted]

BASDAI change from baseline – fixed effects

Figure 16 [redacted]

Figure 16: BASDAI change from baseline expressed as Mean Difference (fixed effects)

BASDAI change from baseline – random effects

Figure 17 [redacted]

[redacted]

Figure 17: BASDAI change from baseline expressed as Mean Difference (random effects)

BASDAI change from baseline – model fit results

[redacted]

Table 46 [redacted]

Table 46: Model comparison for various types of models for BASDAI change from baseline

[redacted]					
[redacted]					
[redacted]					
[redacted]					

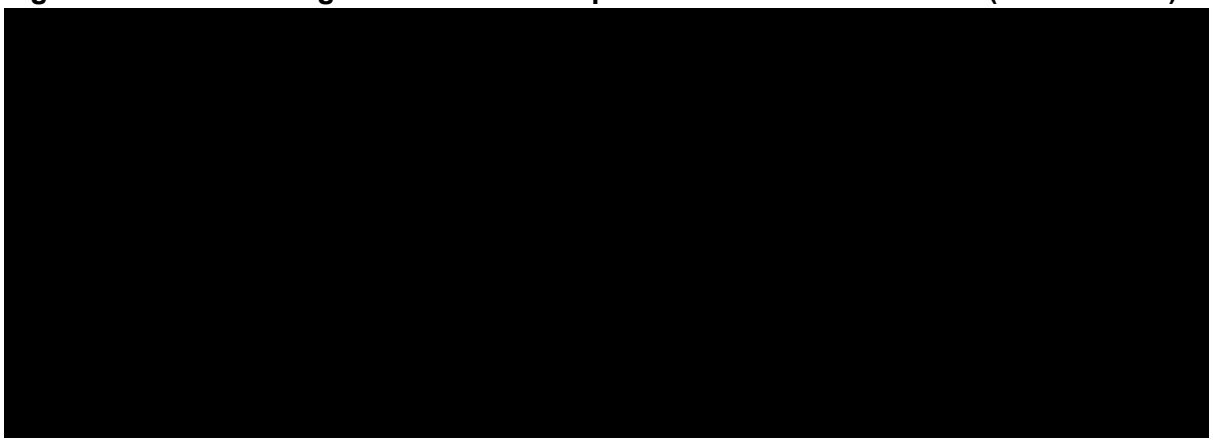
[redacted]

BASFI change from baseline – fixed effects

Figure 18 [redacted]

[redacted]

Figure 18: BASFI change from baseline expressed as Mean Difference (fixed effects)



BASFI change from baseline – random effects

Figure 19 [redacted]

[redacted]

Figure 19: BASFI change from baseline expressed as Mean Difference (random effects)

BASFI change from baseline – model fit results

[redacted]

Table 47 [redacted]

Table 47: Model comparison for various types of models for BASFI change from baseline

[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

Joint modelling of BASFI and BASDAI

[redacted]

Table 48 [redacted]

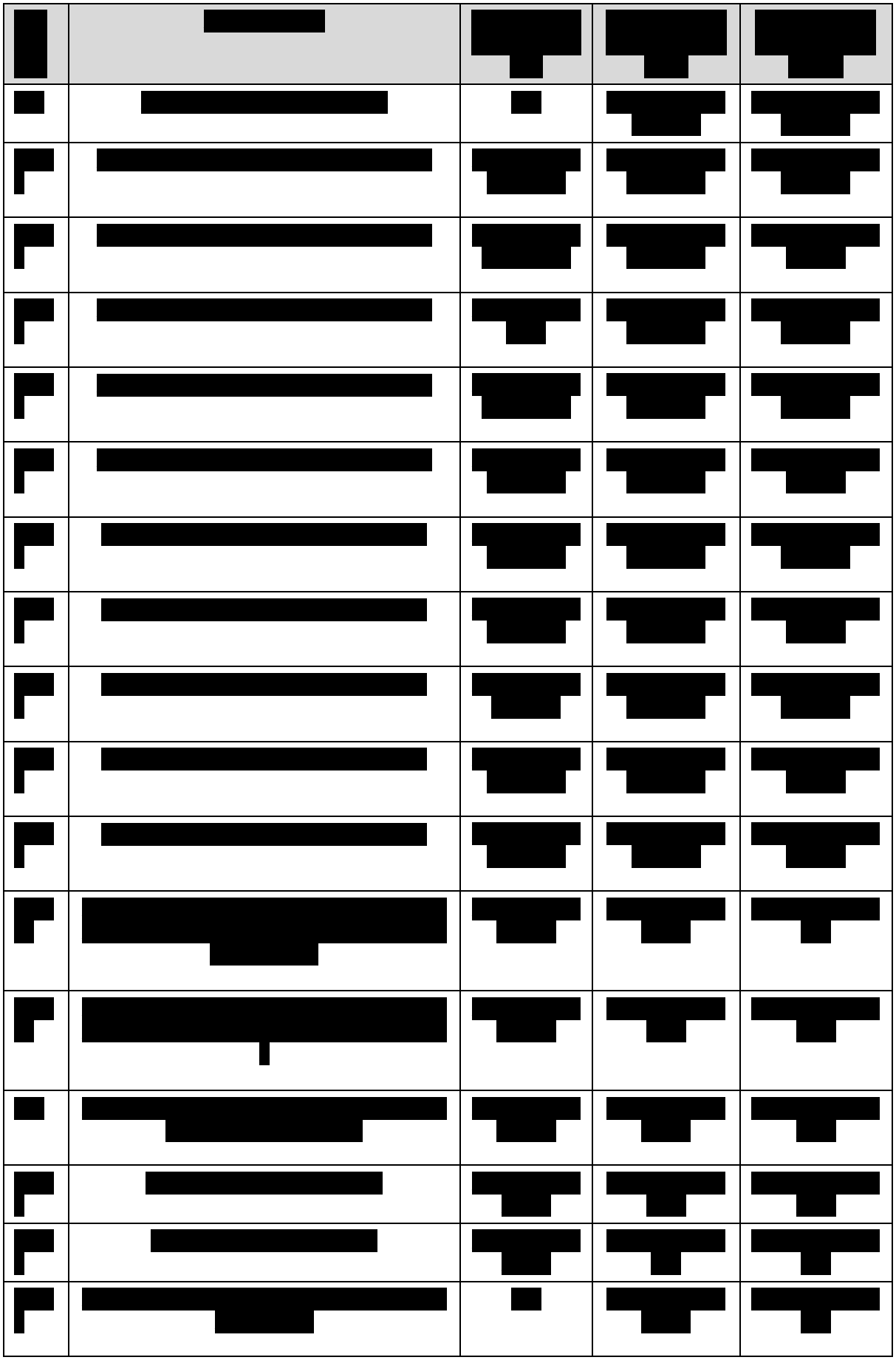
Table 48: Joint BASDAI50 response and BASDAI change from baseline parameter estimates

[redacted]

Table 49 [redacted]

Table 49: Joint correlated BASDAI50, BASDAI change from baseline and BASFI change from baseline parameter estimates

[redacted]



[redacted]

Table 50 [redacted]

Table 50: Table comparing exchangeable effects models for BASDAI change from baseline

[redacted]

Figure 20 – Figure 22 [redacted]

[redacted]

Figure 20: Joint correlated BASDAI50, BASDAI change from baseline and BASFI change from baseline results: estimated BASDAI50 RR vs placebo

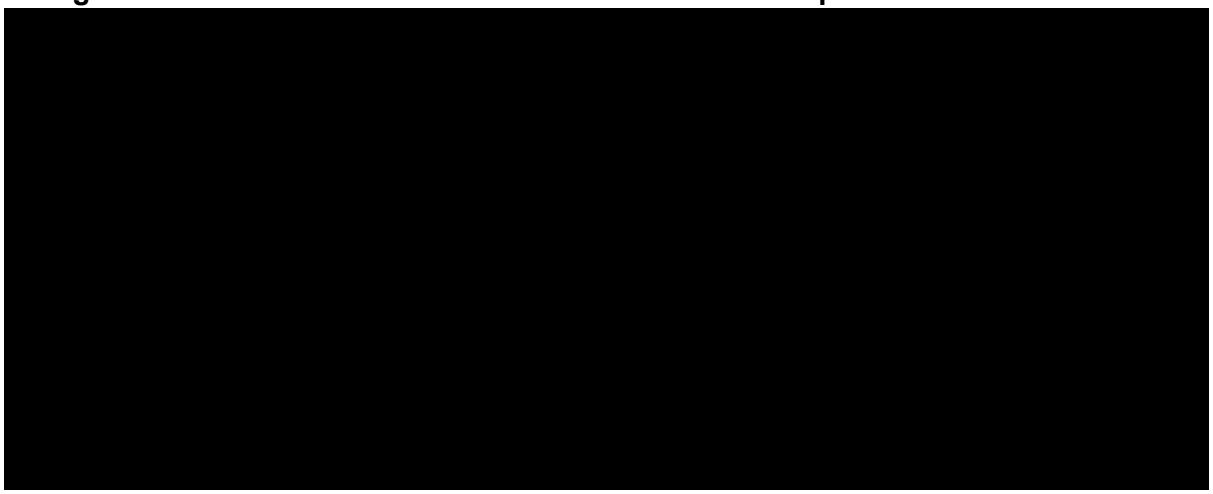


Figure 21: Joint correlated BASDAI50, BASDAI change from baseline and BASFI change from baseline results: estimated BASDAI change from baseline expressed as Mean Difference

Figure 22: Joint correlated BASDAI50, BASDAI change from baseline and BASFI change from baseline results: estimated BASFI change from baseline expressed as Mean Difference

B.2.9.5.2 ***Sensitivity analysis***

Results of sensitivity analyses are presented in Appendix D, and a summary of the rationale for performing these analyses, together with topline results, is provided in Table 51.

Table 51: Summary of NMA sensitivity analyses

Sensitivity analysis	Rationale	Results
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Sensitivity analysis	Rationale	Results
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CrI, credible interval; NMA, network meta-analysis; RR, relative risk; SD, standard deviation;

B.2.9.6 Uncertainties in the indirect and mixed treatment comparisons

Sources of uncertainty are discussed in the sections below.

[redacted]

[redacted]

.2.9.4.3

[redacted]

B.2.9.7 Conclusions

[redacted]

B.2.10 Adverse reactions

Treatment with secukinumab 150 mg (with or without loading) was well tolerated, and no new or unexpected safety signals were identified

- Most AEs reported were mild or moderate in severity for all treatment groups
- AEs up to Week 20 showed [redacted]
- Over the entire treatment period (up to data cut-off of 17th December 2018), [redacted]
- [redacted]

B.2.10.1 PREVENT

Safety results are presented for two separate time periods: the initial period up to Week 20 (Section B.2.10.1.1), and the entire treatment period (up to the data cut-off date of 17-Dec-2018; Section B.2.10.1.2).

Safety results for both analyses (up to Week 20 and the entire treatment period) were evaluated for the following groups:

- Secukinumab 150 mg Load: includes patients randomised at baseline to 150 mg secukinumab SC with loading at baseline and Weeks 1, 2, and 3
- Secukinumab 150 mg No Load: includes patients randomised at baseline to 150 mg secukinumab SC without initial loading

- Any Secukinumab: a combination of the secukinumab 150 mg Load and Secukinumab 150 mg No Load groups; placebo switchers after the switch are also included in this category for analyses of the entire treatment period

- Placebo: includes patients up to Week 20 and those with data past Week 20 who did not switch to open label secukinumab

As per protocol, patients who were deemed to be inadequate responders by Week 20 based on the judgment of the physician and the patient were permitted to switch to secukinumab 150 mg open label. Use of data up to and including the Week 20 last-visit-before-first-switch opportunity provided an unbiased comparison between secukinumab and placebo while data collected beyond Week 20 were included in analyses that summarise the entire treatment period.

The number of patients in the placebo group steadily decreased on account of the switch to open label secukinumab after Week 20. Therefore, any comparison of the secukinumab treatment groups to placebo after Week 20 (i.e. analyses for the entire treatment group) is limited by the small number of patients on placebo and, consequently the lower number of patient-years of exposure to placebo, relative to secukinumab. Exposure-adjusted incidence rates (EAIRs; Table 59 and Table 60) are also presented for the entire treatment period.

Duration of exposure for both secukinumab treatment groups were similar up to the data cut-off. Exposure to placebo treatment had significantly decreased by Week 20 due to the permitted switch. All patients still on placebo were assigned to open label treatment with secukinumab after Week 52. The median duration of exposure was [redacted] for the secukinumab 150 mg Load group, [redacted] for the secukinumab 150 mg No Load group, and [redacted] for the placebo group (Table 52).

Table 52: Duration of exposure to study treatment - entire treatment period (Safety Set)

Exposure	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Any Secukinumab N=524	Placebo N=186
Any exposure	[redacted]	[redacted]	[redacted]	[redacted]
≥12 weeks	[redacted]	[redacted]	[redacted]	[redacted]

≥16 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥20 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥52 weeks	[redacted]	[redacted]	[redacted]	[redacted]
≥104 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Mean, days	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Patient-time (patient years)	[redacted]	[redacted]	[redacted]	[redacted]

Duration of exposure to study treatment was defined as the number of days on the study treatment during the considered period.
Patient-time in patient years was calculated as a sum of individual patient durations in days divided by 365.25.

B.2.10.1.1 *Safety data up to Week 20*

The overall incidence of treatment-emergent adverse events (AEs) up to Week 20 was [redacted] in the composite secukinumab treatment group (Any Secukinumab group, [redacted]) compared with placebo ([redacted]) (Table 53). Although the AEs by system organ class (SOC) showed [redacted] rates in the Any Secukinumab group compared with placebo, most of the differences in rates were [redacted] (< 5%) (Table 54).

Table 53: Absolute and relative frequencies for treatment-emergent AEs by primary SOC (at least 5% in Any Secukinumab) – up to Week 20 (Safety Set)

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Any Secukinumab N=369	Placebo N=186
Primary SOC	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any primary system organ class	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]

A patient with multiple AEs within a primary system organ class is counted only once in the total row.
System organ classes are presented in descending frequency in Any Secukinumab group.
MedDRA Version 21.1 was used for the reporting of AEs.
Abbreviations: AE, adverse event; SOC, system organ class.

Overall, the most commonly reported AEs by preferred term (in the Any Secukinumab group) were [redacted] The frequency of [redacted] All the other most commonly reported AEs were [redacted] As observed for the AEs per SOC, [redacted] (Table 54).

Table 54: Most common treatment-emergent AEs by preferred term (at least 5% in Any Secukinumab) - up to Week 20 (Safety Set)

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Any Secukinumab N=369	Placebo N=186
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any preferred term	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]

A patient with multiple AEs within a preferred term is counted only once in the Any preferred term row.
Preferred terms are presented by descending frequency in the Any Secukinumab group.
A cut-off of 1.0% was used from the Any Secukinumab group.
MedDRA Version 21.1 was used for the reporting of AEs.

Incidence rates reported for serious adverse events (SAEs) up to Week 20 were [redacted] ([redacted] in the Secukinumab 150 mg Load group, [redacted] in the Secukinumab 150 mg No Load group, [redacted] in the Any Secukinumab group, and [redacted] in the placebo group) (Table 55).

Table 55: Absolute and relative frequencies for treatment-emergent SAEs by primary SOC – up to Week 20 (Safety Set)

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Any Secukinumab N=369	Placebo N=186
Primary SOC	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any primary SOC	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]

A patient with multiple AEs within a primary system organ class is counted only once in the total row.
System organ classes are presented in descending frequency in Any Secukinumab group.
MedDRA Version 21.1 was used for the reporting of AEs.
Abbreviations: SAE, serious adverse event; SOC, system organ class.

In the secukinumab 150 mg Load group, all the SAEs were [redacted]

[redacted]

B.2.10.1.2 ***Safety data for the entire treatment period (up to 17th December 2018)***

[redacted]

A summary of key AEs, discontinuations and deaths over the entire treatment period is provided in Table 56.

Table 56: Key AEs, discontinuations and deaths – entire treatment period (Safety set)

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Any Secukinumab N=524†	Placebo N=186
Serious AEs, n/EX (IR)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations due to any AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Deaths, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Selected AEs, n/EX (IR)				
Serious infections/infestations	[redacted]	[redacted]	[redacted]	[redacted]
Inflammatory bowel disease	[redacted]	[redacted]	[redacted]	[redacted]
MACE (myocardial infarction, Stroke, CV death)	[redacted]	[redacted]	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]	[redacted]	[redacted]

†Any Secukinumab column includes also events after switch from patients switching to AIN 150mg from Placebo.
Abbreviations: AE, adverse event; CV, cardiovascular; EX, exposure in patient years; IR, incidence rate per 100 patient years; MACE, major adverse cardiovascular event.

Treatment-emergent AEs in the Any Secukinumab group were reported with [redacted] compared with the placebo group ([redacted] in the Any Secukinumab group and [redacted] in the placebo group) (Table 57).

Table 57: Absolute and relative frequencies for treatment-emergent AEs by primary SOC (at least 5% in Any Secukinumab) – entire treatment period (Safety Set)

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Any Secukinumab N=524	Placebo N=186
Primary SOC	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any primary SOC	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]

A patient with multiple AEs within a primary SOC is counted only once in the total row.
SOCs are presented in descending frequency in Any Secukinumab group.
MedDRA Version 21.1 was used for the reporting of AEs.
Abbreviations: AE, adverse event; SOC, system organ class.

[redacted] were the most commonly reported AEs in the secukinumab treatment groups (Table 58).

Table 58: Most common treatment-emergent AEs by preferred term (at least 5% in Any Secukinumab) – entire treatment period (Safety Set)

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Any Secukinumab N=524	Placebo N=186
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any preferred term	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]

A patient with multiple AEs within a preferred term is counted only once in the Any preferred term row.
Preferred terms are presented by descending frequency in the Any Secukinumab group.
A cut-off of 1.0% was used in the Any Secukinumab group.
MedDRA Version 21.1 was used for the reporting of AEs.

Exposure-adjusted incidence rates for treatment-emergent AEs for the entire treatment period are shown in Table 59. The overall EAIR (per 100 patient years [PY]) of AEs by SOC was [redacted]

Treatment comparisons of secukinumab to placebo for the entire treatment period, however, must be interpreted with caution, in case the reported event rates are not constant over time. As noted above, overall exposure was [redacted] patient years for Any Secukinumab and [redacted] patient years for placebo (Table 52). Moreover, reporting rates, depending on types of AEs, may vary from the initial trial period, with very frequent study visits compared with later study periods with less frequent visits.

The Secukinumab 150 mg Load group had [redacted] EAIRs compared with the Secukinumab 150 mg No Load group ([redacted]).

This was mainly due to differences in

[redacted]).

Table 59: Exposure-adjusted incidence rates for treatment-emergent AEs by primary SOC (at least 5.0 per 100 PY in Any Secukinumab) – entire treatment period (Safety Set)

Primary SOC	Secukinumab 150 mg Load N=185 n/EX (IR)	Secukinumab 150 mg No Load N=184 n/EX (IR)	Any Secukinumab N=524 n/EX (IR)	Placebo N=186 n/EX (IR)
Any primary SOC	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]

Primary system organ classes are sorted by descending frequency in Any Secukinumab group.
A patient with multiple TEAEs within a primary system organ class (PSOC) is counted only once in the PSOC.
For patient with event, exposure time is censored at time of first event.
Comparisons between active regimens and placebo should be viewed with caution due to limited number of patients with long-term placebo data. Valid comparisons are subject to the assumption of constant risk across the entire treatment period, which may not be the case for all AEs.
MedDRA version 21.1 was used for reporting.
Abbreviations: AE, adverse event; EX, exposure in patient years; IR, incidence rate per 100 patient years; SOC, system organ class.

Similar to the reported AEs (by PT) for Week 20,

[redacted] (Table 60).

Table 60: Exposure-adjusted incidence rates for most common treatment-emergent AEs by preferred term (at least 5.0 per 100 PY in Any Secukinumab) – entire treatment period (Safety Set)

Preferred term	Secukinumab 150 mg Load N=185 n/EX (IR)	Secukinumab 150 mg No Load N=184 n/EX (IR)	Any Secukinumab N=524 n/EX (IR)	Placebo N=186 n/EX (IR)
Any Preferred term	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]

Preferred terms are presented in descending order of frequency in the ANY Secukinumab column.
EX=exposure in patient years. IR=incidence rate per 100 patient years.
For patient with an event, exposure time was censored at time of first event.
MedDRA Version 21.1 was used for the reporting of AEs.

Treatment-emergent SAEs were reported for [redacted] of patients in the Any Secukinumab group ([redacted] in the Secukinumab 150 mg Load group, [redacted] in the Secukinumab 150 mg No Load group) and [redacted] of patients in the placebo group. Frequencies were [redacted] between groups for individual SAEs per SOC.

The most common SAEs reported by SOC for the entire treatment group (Any Secukinumab) were

[redacted]

[redacted]

Table 61: Absolute and relative frequencies for treatment-emergent SAEs by primary SOC – entire treatment period (Safety Set)

	Secukinumab 150 mg Load N=185	Secukinumab 150 mg No Load N=184	Any Secukinumab N=524	Placebo N=186
Primary SOC	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any primary SOC	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]	[redacted]	[redacted]

Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]

A patient with multiple AEs within a primary system organ class is counted only once in the total row.
System organ classes are presented by descending frequency in the Any Secukinumab group.
MedDRA Version 21.1 was used for the reporting of AEs.
Abbreviations: AE, adverse event; SOC, system organ class.

For the entire treatment period, [redacted] of patients in the Any secukinumab group and [redacted] of patients in the placebo group had AEs causing study drug discontinuation.

Individual AEs occurred at [redacted].

[redacted]

B.2.10.2 Additional studies

Overall, more than 250,000 patients worldwide have been treated with secukinumab (78). An overview of the pooled long-term safety of secukinumab in patients with moderate-to-severe psoriasis, psoriatic arthritis and ankylosing spondylitis has recently been published (79).

The integrated clinical trial safety dataset includes data pooled from 21 randomised controlled clinical trials of secukinumab 300 mg, 150 mg or 75 mg in the following indications:

- moderate-to-severe psoriasis (14 Phase 3 trials and 1 Phase 4 trial; 5,181 patients; 10,416.9 patient-years)
- psoriatic arthritis (3 Phase 3 trials; 1380 patients; 3866.9 patient-years)
- ankylosing spondylitis (3 Phase 3 trials; 794 patients; 1943.1 patient-years).

The dataset also includes post-marketing safety surveillance data with a cut-off date of June 25, 2017 (cumulative exposure ~ 96,054 patient-years).

The most frequent AE was upper respiratory tract infection. Exposure-adjusted incidence rates across moderate-to-severe psoriasis, psoriatic arthritis and ankylosing spondylitis indications were generally low for serious infections (1.4, 1.9, and 1.2, respectively), Candida infections (2.2, 1.5, and 0.7, respectively), inflammatory bowel disease (0.01, 0.05, and 0.1, respectively), and major adverse cardiac events (0.3, 0.4, and 0.6, respectively). No cases of tuberculosis reactivation were reported. The incidence of treatment-emergent anti-drug antibodies was low with secukinumab across all studies, with no discernible loss of efficacy, unexpected alterations in pharmacokinetics, or association with immunogenicity-related AEs

Secukinumab demonstrated a favourable safety profile over long-term treatment in patients with moderate-to-severe psoriasis, psoriatic arthritis and ankylosing spondylitis. This pooled analysis demonstrates that the safety profile of secukinumab is consistent with previous reports in patients with moderate-to-severe psoriasis, psoriatic arthritis and ankylosing spondylitis, supporting its long-term use in these chronic conditions.

B.2.10.3 Safety overview

Overall, treatment with secukinumab 150 mg (with or without loading) was well tolerated in patients with nr-axSpA, and no new or unexpected safety signals were identified. [redacted]

Most AEs reported up to Week 20 and for the entire treatment period were [redacted] The overall incidence of treatment-emergent AEs up to Week 20 was [redacted] for the secukinumab group (Any Secukinumab group, [redacted]) compared with placebo ([redacted]). Although the AEs by SOC showed [redacted] for secukinumab compared with placebo, most differences in rates were [redacted] (<5%) (Table 53). By Week 20, patients in the Secukinumab 150 mg Load group ([redacted]) reported [redacted] compared with the Secukinumab 150 mg No Load group ([redacted]), due to [redacted].

Over the entire treatment period, [redacted] rates of treatment-emergent AEs were reported for the Secukinumab 150 mg Load group compared with the Secukinumab 150 mg No Load group ([redacted] vs [redacted], respectively). [redacted] accounted for this difference (Secukinumab 150 mg Load: [redacted] vs Secukinumab 150 mg No Load: [redacted]).

Overall EAIRs of AEs by SOC were [redacted] in the secukinumab group compared with placebo (Any Secukinumab: [redacted] per 100 PY vs placebo: [redacted] per 100 PY). EAIRs for [redacted] ([redacted] per 100 PY in the Any Secukinumab group vs [redacted] per 100 PY in the placebo group) contributed the most to this imbalance (Table 7). However, caution should be exercised when interpreting the EAIRs due to the large imbalances in the number of patients and exposure time between secukinumab and placebo groups.

Severe AEs by Week 20 were reported at [redacted] frequencies between treatment groups ([redacted] in the Secukinumab 150 mg Load group, [redacted] in the Secukinumab 150 mg No Load group, and [redacted] in the placebo group). Severe events were [redacted] in all groups over the entire treatment period, however, [redacted] (Any Secukinumab: [redacted] vs placebo: [redacted]).

Frequencies of non-fatal SAEs and discontinuations were [redacted] between the secukinumab and placebo groups up to Week 20. Over the entire treatment period, non-fatal SAEs occurred [redacted] in the Secukinumab 150 mg Load group compared with the Secukinumab 150 mg No Load group and placebo ([redacted] vs [redacted] and [redacted], respectively). Discontinuations due to AEs were [redacted] in the Secukinumab 150 mg No Load group compared with the Secukinumab 150 mg Load group and placebo ([redacted] vs [redacted] and [redacted] respectively).

Incidence rates reported for SAEs up to Week 20 were of low frequency and were [redacted] treatment groups (Secukinumab 150 mg Load group: [redacted], Secukinumab 150 mg No Load group: [redacted], and placebo: [redacted]). The most commonly reported SAEs for secukinumab were from [redacted] SOCs.

EAIRs for treatment-emergent SAEs over the entire treatment period were [redacted] in the secukinumab group compared with placebo (Any Secukinumab group: [redacted] per 100 PY vs placebo group: [redacted] per 100 PY). [redacted] exposure-adjusted incidence rates were observed in the Secukinumab 150 mg Load group compared with the Secukinumab 150 mg No Load group ([redacted] per 100 PY vs [redacted] per 100 PY, respectively).

B.2.11 Ongoing studies

SKIPPAIN (NCT03136861) is 24-week, randomised, double-blind, placebo-controlled, multicentre study due to report in 2020. It is designed to evaluate the efficacy and safety of secukinumab 150 mg compared with placebo in the early management (Baseline to Week 8) of spinal pain, disease activity, fatigue and predictability of disease flares in patients with axial spondyloarthritis who have an inadequate response to prior NSAIDs. This study will also assess the efficacy and safety of secukinumab 300 mg compared with secukinumab 150 mg from Week 8 to Week 24 in order to assess the potential additional benefits of dose escalation in patients with axSpA.

ACHILLES (NCT02771210) is a 52-week randomised, double-blind, placebo-controlled, multicentre study. It is designed to evaluate the efficacy and safety of

secukinumab 150 mg and 300 mg compared with placebo for the treatment of enthesitis at the Achilles tendon in adult patients with active psoriatic arthritis and ax-SpA.

B.2.12 Innovation

Secukinumab is a step-change in the management of nr-axSpA, as it is anticipated to be the first alternative to TNFα inhibitors. The availability of a treatment with a new mode of action will provide increased choice for both patients and clinicians. As described in Section B.1.3.9, limitations in treatment efficacy, safety and impact on quality of life with TNFα inhibitors means that a significant unmet need exists.

[redacted]

B.2.13 Interpretation of clinical effectiveness and safety evidence

Efficacy

PREVENT is the largest trial (N=555) of treatments in patients with nr-AxSpA (60). This pivotal Phase 3 study utilised a double-blind, randomised, placebo-controlled design with two different regimens: secukinumab 150 mg (with and without loading). Overall, both regimens reduced the signs and symptoms of nr-axSpA in a study population consisting primarily of TNFα-naïve patients (90% for the 16-week analyses). Onset of treatment response in the first 4 weeks tended to be faster with the secukinumab 150 mg Load regimen compared with the No Load regimen. However, both secukinumab regimens were efficacious vs placebo in patients with nr-axSpA through all clinical outcomes, including physical function and quality of life measures, and biological markers of disease activity, including hsCRP and ESR.

The efficacy of both secukinumab 150 mg regimens was apparent early (between Week 1 and Week 8) and was sustained up to Week 52. The treatment effects were [redacted] Based on inclusion criteria all patients enrolled into this trial were required to have objective signs of inflammation based either on the presence of abnormal CRP or findings of SI-joint inflammation on MRI at baseline. [redacted]

Safety

The safety profile of secukinumab in PREVENT was based on a cumulative exposure of [redacted] patient years for the secukinumab 150 mg Load group and [redacted] patient years for the secukinumab 150 mg No Load group (compared with [redacted] patient years for the placebo group) and showed no new or unexpected safety signals. [redacted] The exposure-adjusted incidence rate (EAIR, per 100 patient years) for treatment-emergent AEs for the entire treatment period was [redacted] in the any secukinumab group compared with placebo ([redacted] vs [redacted]), primarily due to [redacted]). However, comparisons of secukinumab with placebo for the entire

treatment period should be interpreted with caution due to the limited number of patients with long-term placebo data, as placebo patients, per protocol, were allowed to switch to open label secukinumab after the Week 20 assessments.

[redacted]

Safety observations from PREVENT are consistent with results from an analysis of pooled long-term safety data, in which secukinumab demonstrated a favourable safety profile (Section B.2.10.2).

B.3 Cost effectiveness

The cost-effectiveness analysis showed that secukinumab 150 mg has comparable or improved cost-effectiveness versus conventional care when compared against currently approved biologics

- The economic evaluation compared secukinumab with all approved TNFα inhibitors in nr-axSpA and conventional care (CC) in the biologic-naïve population (primary analysis), and compared secukinumab against CC in the biologic-experienced population (secondary analysis)
- The results of the primary analysis (biologic-naïve patients) showed secukinumab to be the biologic associated with the lowest overall costs
- Only adalimumab biosimilar was associated with a lower incremental cost-effectiveness ratio (ICER) vs CC than secukinumab; however, the results were similar (£5,445 and £7,459 per quality-adjusted life year [QALY] gained, respectively)
- In the secondary analysis (biologic-experienced patients), secukinumab was shown to be dominant compared with CC, [redacted]
- Recommendations issued by NICE in TA383 and TA497 included statements that if more than one treatment is considered suitable, the least expensive should be chosen; adopting similar wording for guidance on secukinumab would ensure that the best value biologic is used in clinical practice

B.3.1 Published cost-effectiveness studies

B.3.1.1 Identification of studies

An SLR was conducted to identify cost-effectiveness studies relevant to the decision problem from the published literature. A complete description of the search strategy is presented in Appendix G.

B.3.1.2 Description of identified studies

No previously published cost-effectiveness studies of secukinumab for nr-axSpA were identified. The SLR identified 10 studies that met the pre-defined inclusion

criteria. Five of these were UK-based studies; these are therefore considered to be relevant to clinical practice in England and are summarised in Appendix G.

B.3.2 Economic analysis

No existing economic evaluations of secukinumab in nr-axSpA were identified in the cost-effectiveness SLR (Section B.3.1); it was therefore necessary to develop a de novo cost-effectiveness model. Economic evaluations used in previous NICE appraisals in nr-axSpA and AS (16, 44, 80) were used to inform the de novo model's structure, assumptions and data sources.

B.3.2.1 Patient population

The cost-effectiveness model considers the population of adult patients (≥18 years) with nr-axSpA, as defined by the 2009 ASAS Classification Criteria (Section B.1.3.2), who have objective signs of inflammation (sacroiliitis on MRI and/or high levels of CRP), whose disease has responded inadequately to, or who are intolerant to, ≥2 NSAIDs. This population is aligned with the population considered in PREVENT (the pivotal clinical trial; Section B.2.3), the anticipated marketing authorisation extension, and the final scope issued by NICE.

The primary analysis considers the population of those who have not previously received biologic treatment (biologic-naïve); this is the population considered in NICE appraisals TA383 and TA407. A secondary analysis is considered based on the population of those who have previously received biologic treatment (biologic-experienced).

B.3.2.2 Model structure

The economic model is structured as a short-term decision tree (induction period) followed by a long-term Markov model (long-term period). This structure is similar to the models presented in TA383 and TA407. A cycle length of 3 months is assumed, and half-cycle correction is applied.

A lifetime time horizon (assuming a maximum age of 100 years) is modelled, in line with current NICE guidelines (81) and previous appraisals in nr-axSpA (16); nr-axSpA is a progressive and chronic condition, with cost and quality of life consequences spanning the lifetime of patients. Scenario analyses are included

considering time horizons of 5, 10, 20 and 40 years. An annual discount rate of 3.5% is applied to costs and outcomes, in line with NICE guidance (81).

Death is an absorbing state and patients can transition to the ‘dead’ state from any other health state.

B.3.2.2.1 *Induction period*

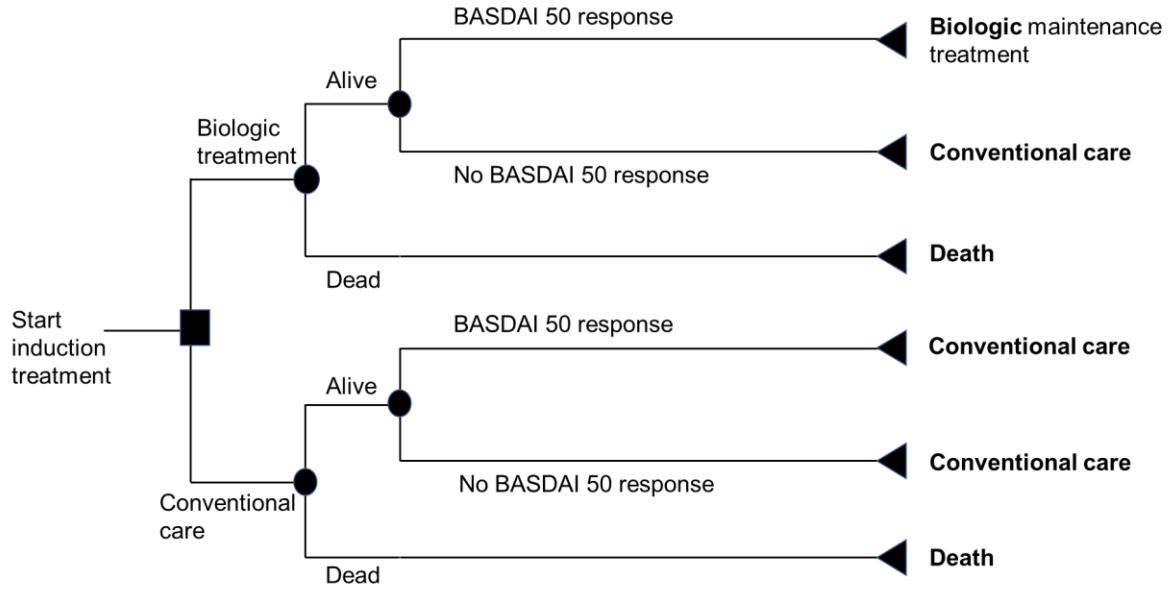
In the induction period, patients enter the model and receive three months of induction treatment; three months was considered a reasonable approximation to the expected induction period, given that a 12-week stopping rule is applied for TNFα inhibitors and a 16-week stopping rule is applied for secukinumab.

At the end of this induction period, patients are assessed for BASDAI50 response and enter the Markov model. Those who do not achieve a BASDAI50 response (non-responders) discontinue from their initial treatment. Those who achieve a BASDAI50 response (responders) continue with the same biologic therapy. BASDAI50 was selected as the definition of response on the basis that:

- BASDAI50 was used as the measure of response in the assessment group model for TA383 (TNFα inhibitors in nr-axSpA and AS), and was accepted by the committee in TA407 (secukinumab in AS)
- BASDAI50 or an absolute change of 2 in BASDAI score was recommended as the measure of response by the ASAS working group (82)
    - However, it is not possible to consider the 2-point change in BASDAI due to a lack of comparator data.

A scenario is considered in which response is based on ASAS40 (the primary endpoint in PREVENT). A schematic of the decision tree is presented in Figure 23.

Figure 23: Decision tree schematic†



†In the scenario in which treatment sequencing is considered (biologic-naïve population only; Section B.3.2.2.2), patients who do not respond to biologic treatment at 3 months are assumed to receive second-line biologic therapy.

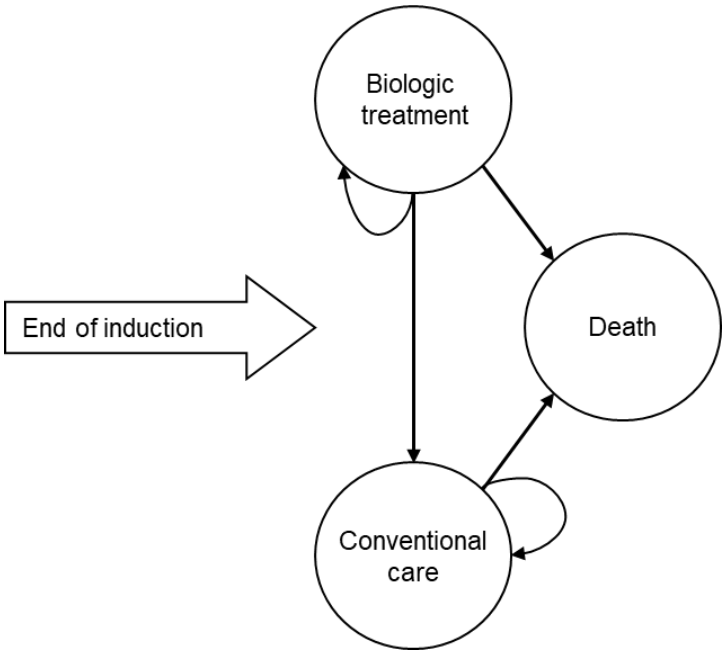
B.3.2.2.2 *Long-term period*

Following assessment of response at 3 months, individuals enter the Markov model (Figure 24). The Markov model consists of two possible pathways, depending on assumptions around treatment sequencing. Treatment sequencing was not considered in the base-case, as no data are available on second-line biologic treatment with TNFα inhibitors; treatment sequencing was not considered in the assessment group model for TA383, and only one company participating in the multiple technology appraisal for TA383 considered treatment sequencing.

However, it is known that TNFα inhibitors are used in biologic-experienced patients in clinical practice [16], and this assumption is therefore considered in an exploratory scenario.

In the base-case, following either non-response at 3 months, or subsequent discontinuation from maintenance therapy, patients move on to conventional care (CC).

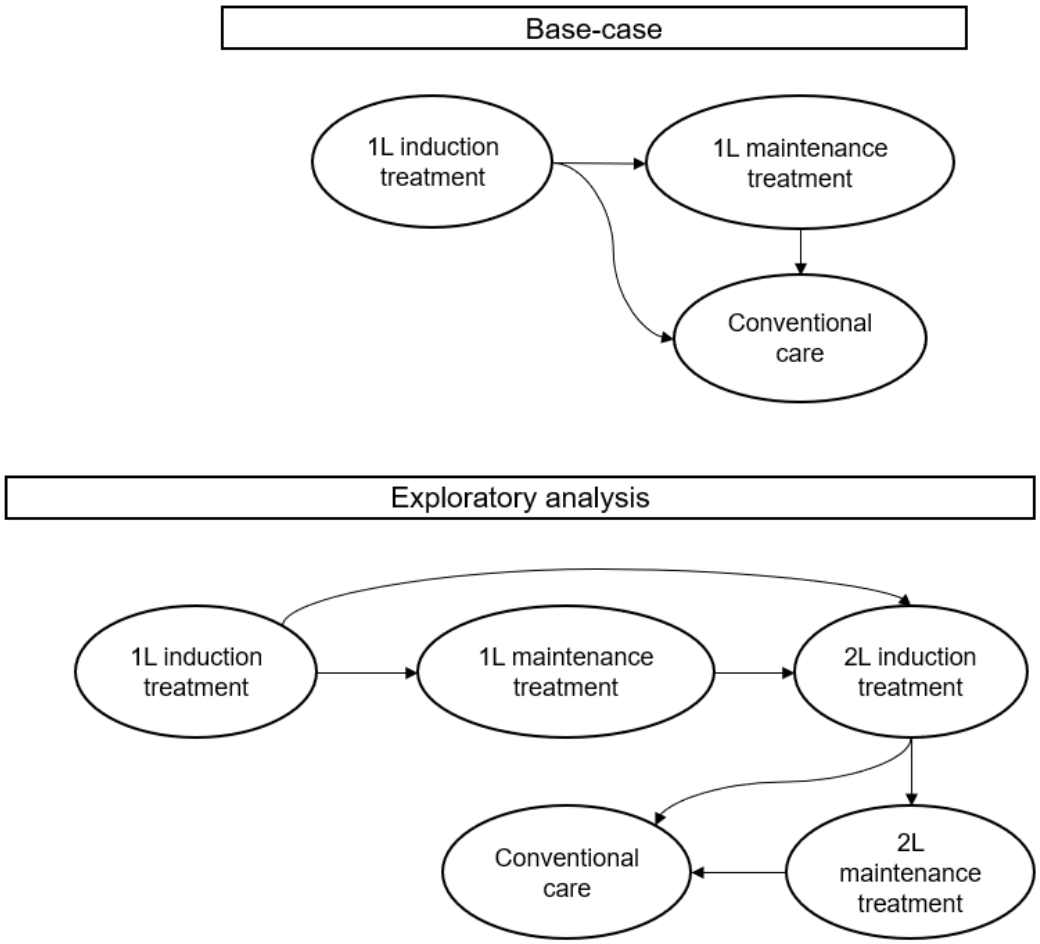
Figure 24: Markov model schematic



In the exploratory scenario analysis, treatment with a second-line biologic therapy is considered following either non-response at 3 months, or discontinuation from first-line maintenance therapy. All modelled patients are assumed to receive a 'mixed basket' of second-line biologic therapies, excluding the first-line biologic received; the composition of this mixed basket is based on market share data[d] (83). Although in clinical practice it may be expected that only a proportion of patients would receive second-line biologic therapy, the scenario in which all patients receive second-line biologic therapy may be expected to provide a 'book-end' estimate of cost-effectiveness (i.e. the true estimate of cost-effectiveness may be expected to lie between the results for the base-case analysis and this exploratory scenario analysis). Response to second-line biologic therapy is assessed at 3 months following second-line induction therapy, after which patients either respond and continue on second-line maintenance therapy until treatment discontinuation, and subsequently transition to CC, or don't respond and transition to CC.

[d] Note that available market share data does not differentiate by line of use.

Figure 25: Treatment pathway, with and without biologic sequencing scenario



Abbreviations:1L, first-line; 2L, second-line.

Utility values and disease management costs were determined based on disease progression, as defined by changes in BASDAI and/or BASFI over time. This is in line with the approach taken in both TA383 and TA407.

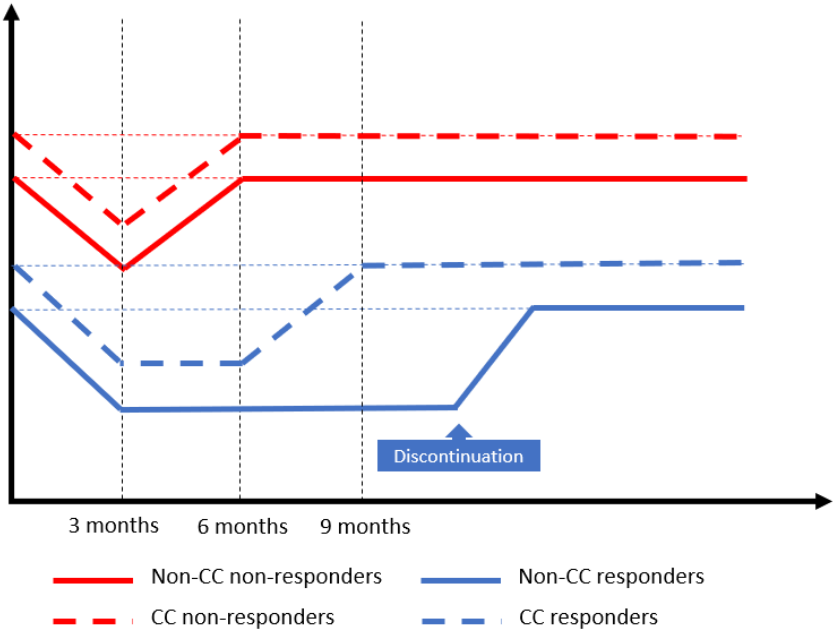
Assumptions relating to how BASFI and BASDAI change over time in the model are presented in Table 62. Illustrative diagrams demonstrating how BASDAI and BASFI are assumed to change over time are presented in Figure 26 and Figure 27, respectively.

Table 62: BASDAI and BASFI over time

	BASDAI				BASFI			
	Biologic responders	**Biologic non-responders**	**CC responders**	**CC non-responders**	**Biologic responders**	**Biologic non-responders**	**CC responders**	**CC non-responders**
First-line baseline	Specific to responders and type of biologic	Specific to non-responders and type of biologic	Specific to CC responders	Specific to CC non-responders	Specific to responders and type of biologic	Specific to non-responders and type of biologic	Specific to CC responders	Specific to CC non-responders
Second-line baseline (scenario only)	Same as first-line baseline	Same as first-line baseline	N/A	N/A	BASFI following discontinuation (i.e. initial gain reversed†) at median cycle of discontinuation from first-line therapy		N/A	N/A
First-line induction period	Specific to responders and type of biologic	Specific to non-responders and type of biologic	Specific to CC responders	Specific to CC non-responders	Specific to responders and type of biologic	Specific to non-responders and type of biologic	Specific to CC responders	Specific to CC non-responders
Second-line induction period (scenario only)	Reduction applied to changes in the first-line induction period		N/A	N/A	Reduction applied to changes in the first-line induction period		N/A	N/A
Long-term period, pre-discontinuation	Remains constant over time		Reverses initial gain† at 3 months; thereafter remains constant over time		Increases at a biologic-specific rate‡ over time		Reverses initial gain† at 3 months; thereafter increases at a CC-specific rate over time	
Long-term period, post-discontinuation	Reverses initial gain†; thereafter remains constant over time				Reverses initial gain†; thereafter increases at a CC-specific rate over time			

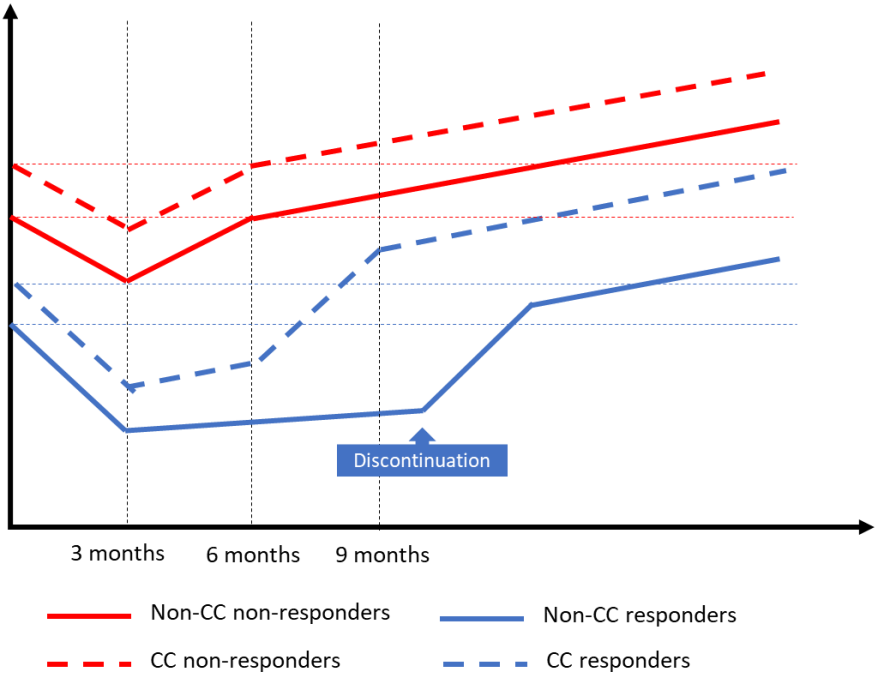
† A scenario is considered in which BASFI and BASDAI revert to natural history (i.e. to the scores that would have been experienced in the absence of treatment) following discontinuation from biologic therapy instead of reversing initial gain. This scenario was not considered clinically plausible by clinicians consulted as part of TA383; ‡ Scenarios are considered in which a) BASFI increases at a CC-specific rate for the first 4 years in those on biologic maintenance treatment, after which a biologic-specific rate is assumed (i.e. the impact of biologics on the rate of change of BASFI compared with CC is not observed until after 4 years) – this scenario was not considered clinically plausible by clinicians consulted as part of TA383; b) BASFI increases at a CC-specific rate for the full time horizon in those on biologic maintenance treatment (i.e. there is no impact on the rate of change of BASFI for biologics compared with CC).
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care.

Figure 26: Illustrative change in BASDAI over time†



Abbreviations: CC, conventional care; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.
†The presented scenario reflects the base-case in which initial gain is reversed following non-response or subsequent discontinuation. Diagrams are for illustrative purposes and are not drawn to scale.

Figure 27: Illustrative change in BASFI over time†



Abbreviations: CC, conventional care; BASFI, Bath Ankylosing Spondylitis Functional Index.
†The presented scenario reflects the base-case in which initial gain is reversed following non-response or subsequent discontinuation. Diagrams are for illustrative purposes and are not drawn to scale.

B.3.2.3 Features of the economic analysis

Given that TA497 (golimumab in nr-axSpA) presented a cost-comparison analysis rather than a cost-utility analysis, this appraisal has been excluded from the comparison presented in Table 63.

Table 63: Features of the economic analysis

Factor	Previous appraisals		Current appraisal	
	TNFα inhibitors in nr-axSpA and AS (TA383)	**Secukinumab in AS (TA407)**	**Chosen value in the base case**	**Justification**
Model type	Decision tree followed by Markov model	Decision tree followed by Markov model	Decision tree followed by Markov model	• Consistent with previous models in AS and nr-axSpA
Time horizon	Lifetime	Lifetime	Lifetime	• Nr-axSpA is associated with a chronic impact on costs and quality of life, and is associated with increased mortality • Consistent with previous models in AS and nr-axSpA
Response criteria	BASDAI50 at 12 weeks	BASDAI50 at 12 weeks	BASDAI50 at 12 weeks	• Recommended by the ASAS working group • Consistent with previous models in AS and nr-axSpA
Rebound assumption	Initial gain reversed	Initial gain reversed	Initial gain reversed	• Clinical input in TA383 confirmed that reversal of initial gain was more clinically plausible than rebound to natural history • Consistent with previous models in AS and nr-axSpA
BASFI annual progression (TNFα inhibitor)	0.017	0.034	0.017	• Consistent with previous models in nr-axSpA
BASFI annual progression (CC)	• 0.039 (nr-axSpA) • 0.082 (AS)	0.082	0.039	• Consistent with previous models in nr-axSpA
Treatment discontinuation rate	Constant annual rate: 0.06	Treatment-specific rates for Year 1 and Year 2+ taken	Constant annual rate: 0.06	• Consistent with previous models in nr-axSpA

Factor	Previous appraisals		Current appraisal	
	TNFα inhibitors in nr-axSpA and AS (TA383)	**Secukinumab in AS (TA407)**	**Chosen value in the base case**	**Justification**
		from the published literature		
AEs	Serious infections	Serious infections	Serious infections and NMSC	• Based on a review by Corbett et al. (77)
Source of utilities	Utility model based on age, sex, BASDAI, BASFI, BASDAI^2, BASFI^2, BASDAI x BASFI	Utility model based on age, sex, BASDAI, BASFI	Utility model based on BASDAI, BASFI, BASDAI x BASFI	• A range of models were considered, and the best fitting model included only BASDAI, BASFI and BASDAI x BASFI as covariates
Costs included	Drug acquisition, administration and monitoring Disease management AEs	Drug acquisition, administration and monitoring Disease management AEs	Drug acquisition, administration and monitoring Disease management AEs	• All costs expected to differ between the compared technologies included • Consistent with previous models in AS and nr-axSpA

Abbreviations: ADA, adalimumab; AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; ETN, etanercept; GOL, golimumab; INF, infliximab, NMSC, non-melanoma skin cancer; nr-axSpA, non-radiographic axial spondyloarthritis; SEC, secukinumab.

B.3.2.4 Intervention technology and comparators

The intervention considered in the model is secukinumab 150 mg. Secukinumab is administered subcutaneously, by a trained professional at first administration, followed by home administration for subsequent doses.

In biologic-naïve patients, secukinumab is compared against all approved TNFα inhibitors in nr-axSpA and CC (i.e. NSAIDs and physiotherapy); no costs are included for CC, given that all other comparators are considered in addition to CC. The relevant comparators included in the evaluation for the biologic-naïve population are therefore:

- Certolizumab pegol
- Etanercept (including biosimilars)
- Adalimumab (including biosimilars)
- Golimumab

- CC.

The only comparator considered for the biologic-experienced population is CC, given that no randomised data on second or subsequent line use of TNFα inhibitors in nr-axSpA is available; a robust comparison vs TNFα inhibitors was therefore not considered possible.

The dosing and administration of secukinumab and TNFα inhibitors are detailed in Table 64.

Table 64: Drug dosing and administration

Drug	Dose	Administration frequency
Secukinumab	150 mg	At Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing
Certolizumab pegol	200 mg	Once every two weeks
Etanercept†	50 mg	Once weekly
Adalimumab†	40 mg	Once every two weeks
Golimumab	50 mg	Once monthly

† Including biosimilars.

B.3.3 Clinical parameters and variables

Clinical data included in the model are:

- Baseline characteristics
- Response rate
- Short-term change in BASDAI and BASFI
- Long-term changes in BASFI
- Discontinuation
- AEs
- Mortality.

Data for response rates, baseline BASDAI/BASFI and short-term change in BASDAI/BASFI from baseline are taken from the NMA (Section B.2.8). In the base-case, [redacted] Base-case data are presented in Sections B.3.3.2 and B.3.3.3; data for the biologic-experienced

population, assuming a 12-week stopping rule for secukinumab, assuming the ASAS40 response criteria, and for alternative specifications of the NMA are presented in Appendix L.

Given that no comparison is made against TNFα inhibitors in the biologic-experienced population (Section B.3.2.4), this analysis is based on PREVENT data only.

All clinical data for adalimumab biosimilars and etanercept biosimilars are assumed to be the same as for adalimumab and etanercept, respectively.

B.3.3.1 Baseline characteristics

Baseline patient characteristics were taken from the PREVENT trial and are presented in Table 65.

Table 65: Baseline patient characteristics

Parameter	Biologic-naïve	Biologic-experienced
Mean age (years)	39	43
Male (%)	46.1%	44.4%

B.3.3.2 Response rate

Base-case biologic-naïve response rates are presented in Table 66.

In the exploratory scenario analysis in which treatment sequencing is modelled, second-line response rates are assumed to be [redacted]. This is based on the ratio of response rates between biologic-experienced and biologic-naïve patients in PREVENT.

Table 66: BASDAI50 response at 3 months†

Drug	Response rate
Secukinumab	[redacted]
Certolizumab pegol	[redacted]
Etanercept	[redacted]
Adalimumab	[redacted]
Golimumab	[redacted]

CC	[redacted]

† Note that although response is modelled at 3 months, data is available at either 12 weeks (certolizumab pegol, etanercept, adalimumab), 16 weeks (golimumab) or both (secukinumab, CC).
Abbreviations: BASDAI. Bath Ankylosing Spondylitis Disease Activity Index; CC, conventional care.

B.3.3.3 Short-term change in BASDAI and BASFI

Baseline BASDAI and BASFI conditional on response in the biologic-naïve population are presented in Table 67. Changes in BASDAI and BASFI conditional on response[e] are presented in Table 68.

In the exploratory scenario analysis in which treatment sequencing is modelled, second-line changes in BASDAI and BASFI are assumed to be [redacted]. This is based on the ratio of change from baseline between biologic-experienced and biologic-naïve patients in PREVENT.

Table 67: Baseline BASDAI and BASFI

Parameter	Baseline BASDAI		Baseline BASFI	
	Responders	Non-responders	Responders	Non-responders
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]
CC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI. Bath Ankylosing Spondylitis Disease Activity Index; BASFI. Bath Ankylosing Spondylitis Functional Index CC, conventional care.

Table 68: Change from baseline at 3 months† in BASDAI and BASFI

Parameter	BASDAI change from baseline		BASFI change from baseline	
	Responders	Non-responders	Responders	Non-responders
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]
CC	[redacted]	[redacted]	[redacted]	[redacted]

[e] Where baseline BASDAI/BASFI or change in BASDAI/BASFI conditional on response were not available for a TNFα inhibitor, these values were estimated assuming that the ratio of baseline BASDAI/BASFI or change in BASDAI/BASFI is the same for TNFα inhibitors as for secukinumab.

† Note that although response is modelled at 3 months, data is available at either 12 weeks (certolizumab pegol, etanercept, adalimumab), 16 weeks (golimumab) or both (secukinumab, CC).
Abbreviations: BASDAI. Bath Ankylosing Spondylitis Disease Activity Index; BASFI. Bath Ankylosing Spondylitis Functional Index CC, conventional care.

B.3.3.4 Long term change in BASFI

Long-term change in BASFI score is calculated using the Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). The effect of treatment with biologic therapies is calculated by multiplying the annual rate of mSASSS change by the change in BASFI corresponding to a one-unit change in mSASSS (Table 69); this approach was also taken in the assessment group model for TA383 and the company submission for TA407.

Table 69: Long-term changes in BASFI

Parameter	Value
Annual rate of mSASSS change	0.69
BASFI change associated with a 1-unit change in mSASSS	0.057
Effect of biologic treatment	0.42

Source: Corbett et al. 2016 (77).
Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index; mSASSS, Modified Stoke Ankylosing Spondylitis Spinal Score.

B.3.3.5 Discontinuation rates

An annual discontinuation rate of 6% is applied for each comparator, in line with the approach taken by the assessment group for TA383.

B.3.3.6 Adverse events

Modelled AEs include non-melanoma skin cancer (NMSC) and serious infection. These AEs were selected for inclusion in the model on the basis of a systematic review conducted by Corbett et al. (77), which concluded that patients with a range of diseases using TNFα inhibitors over the short term have significantly higher rates of serious infection and NMSC (77). Other AEs were not modelled as they were not expected to have a substantive impact on model results. This approach is consistent with the AEs modelled in TA383 and TA407.

The per cycle probability of each AE for each comparator is presented in Table 70; no AEs were modelled in the CC arm. 5% of serious infections were assumed to be tuberculosis (84).

Table 70: AE probabilities

Drug	Per cycle probability			
	Serious Infection	Source	NMSC	Source
Secukinumab	[redacted]	PREVENT	[redacted]	PREVENT
Certolizumab pegol	0.0068	Sieper et al, 2015 (72)	0.0003	Curtis et al, 2019 (85)
Etanercept	0.0014	Dougados et al, 2014 (46)	0.0000	Dougados et al, 2017 (86)
Adalimumab	0.0061	Van der Heijde et al, 2018 (71)	0.0000	Van der Heijde et al, 2018 (71)
Golimumab	0.0064	Van der Heijde et al, 2015 (87)	0.0000	Sieper et al, 2015 (72)

Abbreviations: NMSC, non-melanoma skin cancer.

B.3.3.7 Mortality

General population mortality data was taken from the Office for National Statistics (88), and a Gompertz model was generated using this data (Table 71); gender-specific relative risks for those with nr-axSpA were applied (Table 72). This approach is consistent with that taken by the assessment group for TA383.

Table 71: Gompertz model of general population mortality

Parameter	Value
Constant	–10.33
Gamma	0.09

Table 72: Relative risk for mortality associated with nr-axSpA by gender (77)

Gender	Relative risk
Male	1.63
Female	1.38

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality of life data from clinical trials

EQ-5D-5L data were collected at Baseline and at Weeks 8, 16, 24, 52 and 76 in the PREVENT trial. In line with current NICE guidance (81), utility scores in the PREVENT trial were calculated by mapping the 5L descriptive system data onto the 3L valuation set developed by Dolan et al. (89). The mapping function developed by van Hout et al. was used (90).

A linear mixed model was used to fit EQ-5D utility scores as a response variable, with the following covariates considered for inclusion:

- Age
- Sex
- BASDAI
- BASFI
- $BASDAI^2$
- $BASFI^2$
- BASDAI x BASFI.

This approach is consistent with the approach taken by the assessment group for TA383.

The analysis was performed on the full analysis set of the PREVENT trial, and models were fitted to data from all visits where EQ-5D-5L, BASDAI and BASFI were assessed at the same time, i.e. Baseline and Weeks 8, 16, 24 and 52.

A supplementary analysis was performed in which regression models were refitted using pooled data from both PREVENT and MEASURE 1/2 (the pivotal trials for secukinumab in AS).

Linear mixed models were used to regress EQ-5D scores on predictors, and a random intercept was included to account for potential intra-subject correlations.

Ten alternative models were considered:

- 5 models based on BASDAI and BASFI:
    - Model 1: BASDAI, BASFI
    - Model 2: BASDAI, BASFI, $BASFI^2$
    - Model 3: BASDAI, BASFI, $BASDAI^2$
    - Model 4: BASDAI, BASFI, BASDAI x BASFI
    - Model 5: BASDAI, BASFI, $BASDAI^2$, $BASFI^2$, BASFI x BASDAI
- 5 models based on BASDAI, BASFI, age and sex:
    - Model 6: BASDAI, BASFI, age, sex
    - Model 7: BASDAI, BASFI, $BASFI^2$, age, sex
    - Model 8: BASDAI, BASFI, $BASDAI^2$, age, sex

- Model 9: BASDAI, BASFI, BASDAI x BASFI, age, sex
- Model 10: BASDAI, BASFI, BASDAI^2, BASFI^2, BASFI x BASDAI, age, sex.

Model 4 (including covariates for BASDAI, BASFI, BASDAI x BASFI) was selected as the best-fitting model on the basis of Akaike information criterion (AIC) and Bayesian information criterion (BIC) (Table 73). However, AIC values for models 2, 3, 4 and 5 were all very similar, indicating that there were only minor differences in model fit between them. Models 6 to 10, which also included age and sex, had consistently worse AIC and BIC values than their corresponding counterparts without age and sex. Further details are provided in the full report (91).

The selected utility model is reported in Table 74.

Table 73: PREVENT model fit

Model		AIC	BIC	Pseudo R^2
Model 1	BASDAI, BASFI	[redacted]	[redacted]	[redacted]
Model 2	BASDAI, BASFI, BASDAI^2	[redacted]	[redacted]	[redacted]
Model 3	BASDAI, BASFI, BASFI^2	[redacted]	[redacted]	[redacted]
Model 4	BASDAI, BASFI, BASDAI x BASFI	[redacted]	[redacted]	[redacted]
Model 5	BASDAI, BASFI, BASFI^2, BASDAI^2, BASDAI x BASFI	[redacted]	[redacted]	[redacted]
Model 6	BASDAI, BASFI, age, sex	[redacted]	[redacted]	[redacted]
Model 7	BASDAI, BASFI, BASDAI^2, age, sex	[redacted]	[redacted]	[redacted]
Model 8	BASDAI, BASFI^2, age, sex	[redacted]	[redacted]	[redacted]
Model 9	BASDAI, BASFI, BASDAI x BASFI, age, sex	[redacted]	[redacted]	[redacted]
Model 10	BASDAI, BASFI, BASDAI^2, BASFI^2, BASDAI x BASFI, age, sex	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BIC, Bayesian Information Criterion.

Table 74: Selected utility model (Model 4)

Covariate	Coefficient	p-value	95% CI	
BASDAI	[redacted]	[redacted]	[redacted]	[redacted]
BASFI	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI x BASFI	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CI, confidence interval.

B.3.4.2 Mapping

Given that EQ-5D-5L data were available from the PREVENT trial, there was no requirement to use mapping.

B.3.4.3 Health-related quality-of-life studies

B.3.4.3.1 *Identification of studies*

An SLR was conducted to identify HRQoL studies relevant to the decision problem from the published literature. A complete description of the search strategy is presented in Appendix H.

B.3.4.3.2 *Description of identified studies*

The SLR identified 48 studies that met the pre-defined inclusion criteria. However, only one of these studies was a UK-based study and it only reported an EQ-5D VAS score (92). Therefore, none of the included studies reported specific UK EQ-5D utility values for the model health states.

B.3.4.4 Adverse reactions

Modelled AEs include serious infections (tuberculosis and other serious infections) and NMSC (Section B.3.3.6). A scenario is considered in which AE disutilities are included; the disutilities and AE durations used in this scenario are presented in Table 77.

Table 75: AE disutilities and durations

AE	Disutility	Source of disutility	Duration	Source of duration
Serious infection	–0.156	Stevensen M et al. 2016 (93)	1 month	Stevensen M et al. 2016 (93)
NMSC	–0.0137	Sullivan et al. 2006 (94)	1 month	Expert clinical opinion†

†A conservative estimate of 1 month was applied in the model based on clinical input suggesting an average of 4 to 6 weeks to excision (74); this is considered conservative on the basis that no NMSC events were observed for secukinumab patients in PREVENT. Table 51 and Appendix D provides further information on clinical expert input.
Abbreviations: AE, adverse event; NMSC, non-melanoma skin cancer.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Base-case utility values associated with BASDAI and BASFI are presented in Section B.3.4.1; scenarios are considered using:

- The utility model used by the assessment group for TA383
- The utility model based on pooled data from both PREVENT and MEASURE 1/2 (Section B.3.4.1); and
- The utility model presented by McLeod et al. (95).

AE disutilities implemented in a scenario analysis are presented in Section B.3.4.4.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Identification of studies

An SLR was conducted to identify cost and resource use data relevant to the decision problem from the published literature. A complete description of the search strategy is presented in Appendix I.

B.3.5.2 Description of identified studies

The SLR identified 31 studies that met the pre-defined inclusion criteria. Of these, four were UK-based studies. These are summarised in Appendix I.

Costs considered in the model include those associated with:

- Drug acquisition, administration and monitoring (Section B.3.5.3)
- Disease management (Section B.3.5.4)
- AEs (Section B.3.5.5)

All costs are valued in 2019 UK pounds. Where necessary[f], costs were inflated to 2017/18[g] prices using healthcare-specific inflation indices from the Unit Costs of Health and Social Care, as issued by the Personal Social Services Research Unit (PSSRU) (96).

[f] Only costs from prior to 2018 were inflated; in particular, costs from the most recent releases of the Unit Costs of Health and Social Care and NHS reference costs were not inflated.
[g] The most recent edition of the Unit Costs of Health and Social Care includes inflation indices up to 2017/18.

B.3.5.3 Intervention and comparators' costs and resource use

Drug acquisition costs for secukinumab and TNFα inhibitors were obtained from the British National Formulary (BNF) (97) (Table 76). The only exception to this is the cost for an adalimumab biosimilar, which was assumed to be the interim national reference price set by the NHS England tendering process (98).

The number of administrations assumed for each time period is based on the dosing schedule specified in each technology's summary of product characteristics (SmPC).

Response is assessed at 12 weeks for TNFα inhibitors and 16 weeks for secukinumab; 12 and 16 weeks of costs are therefore assumed for each of TNFα inhibitors and secukinumab, respectively, in the first 3 months. The dose provided on the day of response assessment is assumed to be included; where a dose is scheduled to be administered shortly after 12 or 16 weeks (as for secukinumab and golimumab), this dose is assumed to be included. The number of doses in Months 4–6 is adjusted to give the correct annual number of doses. A scenario is considered in which response is assessed at 12 weeks for secukinumab, and the number of doses adjusted accordingly.

The cost of administration for each comparator (£45) was taken from the PSSRU Unit Costs of Health and Social Care (96), assuming a one-off, one-hour training session for self-administration with a hospital-based nurse.

No drug acquisition or administration costs are included in the CC arm of the model.

Table 76: Drug acquisition costs

Drug	Dose	Cost per prefilled syringe	Number of administrations		
			First 3 months	Months 4–6	Subsequent 3-month periods
Secukinumab (including PAS)	150 mg	[redacted]	8.00	2.00	3.00
Certolizumab pegol	200 mg	£357.50	0.00†	6.05	6.52
Etanercept	50 mg	£178.75	13.00	13.10	13.04
Adalimumab	40 mg	£352.14	7.00	6.05	6.52
Golimumab	50 mg	£762.97	4.00	2.00	3.00
Etanercept biosimilar	50 mg	£164.00	13.00	13.10	13.04
Adalimumab biosimilar	40 mg	£136.54	7.00	6.05	6.52

† A complex patient access scheme is available for certolizumab pegol in which the first 12 weeks of treatment are borne by UCB.

Monitoring costs associated with secukinumab and TNFα inhibitors are presented in Table 77. All monitoring costs are applied for first-line biologic treatment; in the exploratory analysis in which treatment sequencing is considered, only GP visits and specialist visits are applied for second-line treatment. Resource use is assumed to be the same as in the assessment group model for TA383.

Table 77: Monitoring costs

Resource component	Unit cost	Source of unit cost	Resource use†	
			First 3 months	Subsequent 3-month periods
Specialist visit	£137	Consultant-led non-admitted face to face attendance, follow-up. HRG code Rheumatology WF01A (99)	2	0.5
Full blood count	£3.18	Cost of laboratory tests from York NHS as per TA199 assessment report (2013 costs inflated to 2019) (77, 100)	2	1
Erythrocyte sedimentation rate	£3.15		2	1
Liver function test	£0.80		2	1
Urea and electrolytes	£1.47		2	1
Chest radiograph	£27.94		1	0.25
Tuberculosis Heaf test	£9.30		1	0
Antinuclear antibodies	£4.96		1	0
DNA test	£4.96		1	0
MRI	£154.12		1	0
CRP	£7.06	Henriksson et al, 2010 (101) (inflated to 2019)	1	0

† Resource use is assumed to be the same as in the assessment group model for TA383.
Abbreviations: CRP, C-reactive protein; MRI, magnetic resonance imaging.

B.3.5.4 Health-state unit costs and resource use

Disease management costs are calculated as: $£1{,}370.15 \times \exp(0.213 \times BASFI)$.

This formula reflects that used in the assessment group model for TA383, with the cost component inflated to 2019 prices. Other formulas used to calculate disease management costs in previous NICE appraisals in nr-axSpA and AS are presented

in Table 78. The approaches taken in the TA383 assessment group model and the UCB submission for TA383 were considered most appropriate as these are based on BASFI, which is assumed to change over time, rather than BASDAI which is assumed to remain constant. The approach taken in the assessment group model for TA383 was selected for the model base-case on the basis that this approach was accepted previously.

Table 78: Alternative models of disease management costs

Source	Model of disease management costs
AbbVie submission in TA383 (adalimumab)	£1,124.62 x exp (0.264 x BASDAI)
UCB submission in TA383 (certolizumab pegol)	£1,909.33 x exp (0.1832 x BASFI)
Pfizer submission in TA383 (etanercept)	BASDAI < 40: £151.96 40 ≤ BASDAI < 60: £311.08 BASDAI ≥ 60: £1,039.16
Assessment group model in TA383	£1,284.186 x exp (0.213 x BASFI)

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; UCB, Union Chimique Belge.

B.3.5.5 Adverse reaction unit costs and resource use

Modelled AEs include serious infections (5% tuberculosis) and NMSC (Section B.3.3.6). Costs for treating serious infections are presented in Table 79.

The cost for treating NMSC was found to be £1,626 in 2010 (102); an inflated value of £1,855.63 is used in the model.

Table 79: Serious infection costs (103)

Type of serious infection	HRG code	HRG description	Activity	Unit cost (2017–2018)	Weighted average cost (2017–2018)
Tuberculosis	DZ14F	Pulmonary, Pleural or Other Tuberculosis, with Interventions	668	£4,948	£2,834.68
	DZ14G	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 7+	925	£3,495	
	DZ14H	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 3–6	1,080	£2,659	
	DZ14J	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 0–2	1,501	£1,613	

Type of serious infection	HRG code	HRG description	Activity	Unit cost (2017–2018)	Weighted average cost (2017–2018)
Other serious infection	WJ06J	Sepsis without Interventions, with CC Score 0–4	140,638	£1,410	£1,257.85
	DZ23N	Bronchopneumonia without Interventions, with CC Score 0–5	3,702	£1,105	
	LA04M	Kidney or UTI, with interventions with CC score 0–2	2,319	£2,502	
	DZ22Q	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 0–4	63,106	£709	
	DZ65J	Chronic Obstructive Pulmonary Disease or Bronchitis, without Interventions, with CC Score 0–4	42,795	£1,513	

Abbreviations: HRG, Health-related group; CC, complications and comorbidities; UTI, urinary tract infection;

B.3.5.6 Miscellaneous unit costs and resource use

No additional costs were considered.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of base-case analysis inputs is provided in Table 80.

Table 80: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Age	39	38–40 (normal)	Baseline characteristics, B.3.3.1
Male	46.1%	Not varied	
Cycle length	0.25 years	Not varied	Model structure, B.3.2.2
Discount rate (costs and outcomes)	3.5%	Not varied	
Product share in second-line mixed treatment			
Secukinumab	[redacted]	Not varied	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Certolizumab pegol	[redacted]	Not varied	Model structure, B.3.3.2
Etanercept	[redacted]	Not varied	
Adalimumab	[redacted]	Not varied	
Golimumab	[redacted]	Not varied	
Etanercept biosimilar	[redacted]	Not varied	
Adalimumab biosimilar	[redacted]	Not varied	
Initial BASDAI50 response (12–16 weeks) with secukinumab at week 16, biologic-naïve population			
Secukinumab	[redacted]	[redacted]	Response rate, B.3.3.2
Certolizumab pegol	[redacted]	[redacted]	
Etanercept	[redacted]	[redacted]	
Adalimumab	[redacted]	[redacted]	
Golimumab	[redacted]	[redacted]	
CC	[redacted]	[redacted]	
Etanercept biosimilar	[redacted]	[redacted]	
Adalimumab biosimilar	[redacted]	[redacted]	
Baseline BASDAI and BASFI			
Overall baseline BASDAI	[redacted]	[redacted]	Response rate, B.3.3.2
Overall baseline BASFI	[redacted]	[redacted]	
Baseline BASDAI, responders			
Secukinumab	[redacted]	[redacted]	Response rate, B.3.3.2
Certolizumab pegol	[redacted]	[redacted]	
Etanercept	[redacted]	[redacted]	
Adalimumab	[redacted]	[redacted]	
Golimumab	[redacted]	[redacted]	
CC	[redacted]	[redacted]	
Etanercept biosimilar	[redacted]	[redacted]	
Adalimumab biosimilar	[redacted]	[redacted]	
Baseline BASDAI, non-responders			
Secukinumab	[redacted]	[redacted]	Response rate, B.3.3.2
Certolizumab pegol	[redacted]	[redacted]	
Etanercept	[redacted]	[redacted]	
Adalimumab	[redacted]	[redacted]	
Golimumab	[redacted]	[redacted]	
CC	[redacted]	[redacted]	
Etanercept biosimilar	[redacted]	[redacted]	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Adalimumab biosimilar	[redacted]	[redacted]	
Baseline BASFI, responders			
Secukinumab	[redacted]	[redacted]	Response rate, B.3.3.2
Certolizumab pegol	[redacted]	[redacted]	
Etanercept	[redacted]	[redacted]	
Adalimumab	[redacted]	[redacted]	
Golimumab	[redacted]	[redacted]	
CC	[redacted]	[redacted]	
Etanercept biosimilar	[redacted]	[redacted]	
Adalimumab biosimilar	[redacted]	[redacted]	
Baseline BASFI, non-responders			
Secukinumab	[redacted]	[redacted]	Response rate, B.3.3.2
Certolizumab pegol	[redacted]	[redacted]	
Etanercept	[redacted]	[redacted]	
Adalimumab	[redacted]	[redacted]	
Golimumab	[redacted]	[redacted]	
CC	[redacted]	[redacted]	
Etanercept biosimilar	[redacted]	[redacted]	
Adalimumab biosimilar	[redacted]	[redacted]	
Change in BASDAI at 3 months, responders			
Secukinumab	[redacted]	[redacted]	Short-term change in BASDAI and BASFI, B.3.3.3
Certolizumab pegol	[redacted]	[redacted]	
Etanercept	[redacted]	[redacted]	
Adalimumab	[redacted]	[redacted]	
Golimumab	[redacted]	[redacted]	
CC	[redacted]	[redacted]	
Etanercept biosimilar	[redacted]	[redacted]	
Adalimumab biosimilar	[redacted]	[redacted]	
Change in BASDAI at 3 months, non-responders			
Secukinumab	[redacted]	[redacted]	Short-term change in BASDAI and BASFI, B.3.3.3
Certolizumab pegol	[redacted]	[redacted]	
Etanercept	[redacted]	[redacted]	
Adalimumab	[redacted]	[redacted]	
Golimumab	[redacted]	[redacted]	
CC	[redacted]	[redacted]	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Etanercept biosimilar	[redacted]	[redacted]	
Adalimumab biosimilar	[redacted]	[redacted]	
Change in BASFI at 3 months, responders			
Secukinumab	[redacted]	[redacted]	Short-term change in BASDAI and BASFI, B.3.3.3
Certolizumab pegol	[redacted]	[redacted]	
Etanercept	[redacted]	[redacted]	
Adalimumab	[redacted]	[redacted]	
Golimumab	[redacted]	[redacted]	
CC	[redacted]	[redacted]	
Etanercept biosimilar	[redacted]	[redacted]	
Adalimumab biosimilar	[redacted]	[redacted]	
Change in BASFI at 3 months, non-responders			
Secukinumab	[redacted]	[redacted]	Short-term change in BASDAI and BASFI, B.3.3.3
Certolizumab pegol	[redacted]	[redacted]	
Etanercept	[redacted]	[redacted]	
Adalimumab	[redacted]	[redacted]	
Golimumab	[redacted]	[redacted]	
CC	[redacted]	[redacted]	
Etanercept biosimilar	[redacted]	[redacted]	
Adalimumab biosimilar	[redacted]	[redacted]	
Treatment effect on progression			
Secukinumab	0.42	0.23; 0.7 (lognormal)	Long-term changes in BASFI, B.3.3.4
TNFα inhibitors	0.42	0.23; 0.7 (lognormal)	
CC	1.00	0.78; 1.26 (lognormal)	
Annual withdrawal rates			
Secukinumab	0.6	0.05; 0.07 (beta)	Discontinuation rates, B.3.3.5
Certolizumab pegol	0.6	0.05; 0.07 (beta)	
Etanercept	0.6	0.05; 0.07 (beta)	
Adalimumab	0.6	0.05; 0.07 (beta)	
Golimumab	0.6	0.05; 0.07 (beta)	
Etanercept biosimilar	0.6	0.05; 0.07 (beta)	
Adalimumab biosimilar	0.6	0.05; 0.07 (beta)	
AEs			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Secukinumab – serious infection	[redacted]	[redacted]	AEs, B.3.3.6
Certolizumab pegol – serious infection	0.0068	0.0056; 0.0082 (beta)	
Etanercept – serious infection	0.0014	0.0011; 0.0016 (beta)	
Adalimumab – serious infection	0.0061	0.0049; 0.0073 (beta)	
Golimumab – serious infection	0.0064	0.0052; 0.0077 (beta)	
CC – serious infection	0	Not varied	
Etanercept biosimilar – serious infection	0.0014	0.0011; 0.0016 (beta)	
Adalimumab biosimilar – serious infection	0.0061	0.0049; 0.0073 (beta)	
Secukinumab – NMSC	0	Not varied	
Certolizumab pegol – NMSC	0.0003	0.0002; 0.0003	
Etanercept – NMSC	0	Not varied	
Adalimumab – NMSC	0	Not varied	
Golimumab – NMSC	0	Not varied	
CC – NMSC	0	Not varied	
Etanercept biosimilar – NMSC	0	Not varied	
Adalimumab biosimilar – NMSC	0	Not varied	
Serious infection distribution – Tuberculosis	0.0498	0.04; 0.06 (beta)	
Serious infection distribution – Other serious infection	0.9502	0.65; 1.00 (beta)	
Months of AE disutility – serious infection	1	0.8; 1.2 (normal)	
Months of AE disutility – NMSC	1	1.61; 2.39 (normal)	
Gompertz model of general population mortality			
Constant	–10.3253	Not varied	Mortality, B.3.3.7
Gamma	0.0940	Not varied	
Relative risk for mortality associated with nr-axSpA, Male	1.63	Not varied	Mortality, B.3.3.7
Relative risk for mortality associated with nr-axSpA, Female	1.38	Not varied	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Annual rate of mSASSS change for mSASSS <10			
Secukinumab	0.69	0.63; 0.75 (normal)	Long-term change in BASFI, B.3.3.4
TNFα inhibitors	0.69	0.63; 0.75 (normal)	
CC	0.69	0.63; 0.75 (normal)	
BASFI change with 1 unit change in mSASSS	0.057	0.05; 0.07 (normal)	
Health-related quality of life, linear model			
BASDAI coefficient	–0.032901	[redacted]	Utility model, Table 74, B.3.4.1
BASFI coefficient	–0.010434	[redacted]	
BASDAI x BASFAI coefficient	–0.003194	[redacted]	
Constant	0.835712	[redacted]	
Acquisition costs			
Secukinumab 150 mg	[redacted]	Not varied	Intervention and comparators' costs and resource use, B3.5.3
Certolizumab pegol 200 mg	£357.50	Not varied	
Etanercept 50 mg	£178.75	Not varied	
Adalimumab 40 mg	£352.14	Not varied	
Golimumab 50 mg	£762.97	Not varied	
Etanercept biosimilar 50 mg	£164.00	Not varied	
Adalimumab biosimilar 40 mg	£136.54	Not varied	
Cost of first subcutaneous injection	£45	Not varied	
Dosing – first 3 months			
Secukinumab	8	Not varied	Intervention and comparators' costs and resource use, B3.5.3
Certolizumab pegol	0	Not varied	
Etanercept	13	Not varied	
Adalimumab	7	Not varied	
Golimumab	4	Not varied	
Etanercept biosimilar	13	Not varied	
Adalimumab biosimilar	7	Not varied	
Dosing – 4–6 months			
Secukinumab	2	Not varied	Intervention and comparators' costs and resource use, B3.5.3
Certolizumab pegol	6.05	Not varied	
Etanercept	13.10	Not varied	
Adalimumab	6.05	Not varied	
Golimumab	2.00	Not varied	
Etanercept biosimilar	13.10	Not varied	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Adalimumab biosimilar	6.05	Not varied	
Dosing – Subsequent 3-month periods			
Secukinumab	3.00	Not varied	Intervention and comparators' costs and resource use, B3.5.3
Certolizumab pegol	6.52	Not varied	
Etanercept	13.04	Not varied	
Adalimumab	6.52	Not varied	
Golimumab	3.00	Not varied	
Etanercept biosimilar	13.04	Not varied	
Adalimumab biosimilar	6.52	Not varied	
Monitoring costs			
Full blood count, unit cost	£3.18	2.59; 3.83 (gamma)	Intervention and comparators' costs and resource use, B3.5.3
Erythrocyte sedimentation rate, unit cost	£3.15	2.56; 3.79 (gamma)	
Liver function test, unit cost	£0.80	0.65; 0.96 (gamma)	
Urea and electrolytes, unit cost	£1.47	1.2; 1.77 (gamma)	
Chest radiograph, unit cost	£27.94	22.74; 33.68 (gamma)	
Tuberculosis Heaf test, unit cost	£9.30	7.57; 11.21 (gamma)	
Antinuclear antibodies, unit cost	£4.96	4.04; 5.98 (gamma)	
DNA test, unit cost	£4.96	4.04; 5.98 (gamma)	
MRI, unit cost	£154.12	125.4; 185.76 (gamma)	
CRP, unit cost	£7.06	5.75; 8.51 (gamma)	
Specialist visit, unit cost	£137	111.47; 165.12 (gamma)	
Monitoring, resource use – first 3 months			
Full blood count	2	1.63; 2.41 (gamma)	Intervention and comparators' costs and resource use, B3.5.3
Erythrocyte sedimentation rate	2	1.63; 2.41 (gamma)	
Liver function test	2	1.63; 2.41 (gamma)	
Urea and electrolytes	2	1.63; 2.41 (gamma)	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Chest radiograph	1	0.81; 1.12 (gamma)	
Tuberculosis Heaf test	1	0.81; 1.12 (gamma)	
Antinuclear antibodies	1	0.81; 1.12 (gamma)	
DNA test	1	0.81; 1.12 (gamma)	
X-ray	1	0.81; 1.12 (gamma)	
MRI	1	0.81; 1.12 (gamma)	
CRP	1	Not varied	
Specialist visit	2	1.63; 2.41 (gamma)	
Monitoring, resource use – subsequent 3-month periods			
Full blood count	1	0.81; 1.12 (gamma)	Intervention and comparators' costs and resource use, B3.5.3
Erythrocyte sedimentation rate	1	0.81; 1.12 (gamma)	
Liver function test	1	0.81; 1.12 (gamma)	
Urea and electrolytes	1	0.81; 1.12 (gamma)	
Chest radiograph	0.25	0.2; 0.3 (gamma)	
Tuberculosis Heaf test	0	Not varied	
Antinuclear antibodies	0	Not varied	
DNA test	0	Not varied	
MRI	0	Not varied	
CRP	0	Not varied	
Specialist visit	0.5	0.41; 0.6 (gamma)	
Serious infection cost			
Tuberculosis	£2,834.68	2306.41; 3416.61 (gamma)	Adverse reaction unit costs and resource use, B.3.5.5
Other serious infection	£1,257.85	1023.44; 1516.07 (gamma)	
NMSC	£1,855.63	1509.81; 2236.57 (gamma)	
Health-state costs, active disease			
Intercept	1370.1509	1369.83; 1370.47 (gamma)	Health-state unit costs and

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
BASFI coefficient	0.2130	0.14; 0.29 (beta)	resource use, B.3.5.4

Abbreviations: AE, adverse event; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care; CI, confidence interval; CRP, c-reactive protein; DNA, deoxyribonucleic acid; MRI, magnetic resonance imaging; mSASSS, Modified Stoke Ankylosing Spondylitis Spinal Score; NMSC, non-melanoma skin cancer; TNFα, tumour necrosis factor alpha.

B.3.6.2 Assumptions

A summary of assumptions is provided in Table 81.

Table 81: Assumptions

Assumption	Justification
BASDAI50 is an appropriate measure of response in nr-axSpA.	BASDAI50 was used as the measure of response in the assessment group model for TA383 and was recommended by the ASAS group.
In clinical practice, response is assessed at approximately 3 months	Three months was considered a reasonable approximation to the expected induction period, given that a 12-week stopping rule is applied for TNFα inhibitors, and a 16-week stopping rule is applied for secukinumab.
On biologic maintenance treatment, BASDAI remains constant in all patients.	This assumption is consistent with the approach taken in the assessment group model for TA383.
On biologic maintenance treatment, BASFI increases at a biologic-specific rate over time.	This assumption is consistent with the approach taken in the assessment group model for TA383, and the findings of Corbett et al (77)
Following discontinuation from biologic therapy, the initial gain in BASFI and BASDAI is reversed.	This assumption is consistent with the approach taken in the assessment group model for TA383 and assumes that all patients who don't respond to biologics observe a reversal of their BASDAI and BASFI scores equivalent to the initial gain received at the end of induction treatment. Clinical input in TA383 confirmed that reversal of initial gain was more clinically plausible than rebound to natural history. A scenario is considered in which BASDAI and BASFI revert to natural history following discontinuation from biologic therapy.
After discontinuation from biologic therapy and reversal of initial gain, BASDAI remains constant over time.	This assumption is consistent with the approach taken in the assessment group model for TA383.
After discontinuation from biologic therapy and reversal of initial gain, BASFI increases at a CC-specific rate over time for all patients.	This assumption is consistent with the approach taken in the assessment group model for TA383.
Utility values are a function of BASDAI, BASFI and the interaction of the two.	A similar approach was taken to that of the Pfizer model in TA383, and a range of models were estimated including BASDAI, BASFI, BASDAI x BASFI, $BASDAI^2$, $BASFI^2$, age and sex. The best fitting model was chosen for the base-

Assumption	Justification
	case of the economic evaluation, based on AIC and BIC values.
Disease management costs are a function of BASFI.	This is consistent with the approach taken in TA383. Modelling disease management costs as a function of BASFI rather than BASDAI results in such costs increasing as disease function worsens, as may be expected.

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; nr-axSpA, non-radiographic axial spondyloarthritis; TNFα, tumour necrosis factor alpha.

B.3.7 Base-case results

B.3.8 Base-case incremental cost-effectiveness analysis results

The base-case results for the primary analysis (biologic-naïve patients) and the secondary analysis (biologic-experienced patients) are presented in Table 82 and Table 83, respectively. The results presented for the primary and secondary analyses are not expected to be directly comparable, given that the primary analysis is informed by the NMA, while the secondary analysis uses PREVENT data only.

Table 82: Base-case results (primary analysis – biologic-naïve patients)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)	ICER incremental (£/QALY)
CC	[redacted]	20.42	[redacted]	[redacted]	–	[redacted]	–	–
Secukinumab	[redacted]	20.42	[redacted]	[redacted]	0.00	[redacted]	£7,459	Extendedly dominated
Adalimumab biosimilar	[redacted]	20.42	[redacted]	[redacted]	0.00	[redacted]	£5,445	£5,445
Etanercept biosimilar	[redacted]	20.42	[redacted]	[redacted]	0.00	[redacted]	£18,864	Dominated
Etanercept	[redacted]	20.42	[redacted]	[redacted]	0.00	[redacted]	£21,150	Dominated
Certolizumab pegol†	[redacted]	20.42	[redacted]	[redacted]	0.00	[redacted]	£18,622	£157,868
Golimumab	[redacted]	20.42	[redacted]	[redacted]	0.00	[redacted]	£20,017	£572,694
Adalimumab	[redacted]	20.42	[redacted]	[redacted]	0.00	[redacted]	£22,031	Dominated

† Including the complex patient access scheme available for certolizumab pegol in which the first 12 weeks of treatment are borne by UCB.
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 83: Base-case results (secondary analysis – biologic-experienced patients)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs vs baseline (£)	Incremental LYG vs baseline	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)
CC	[redacted]	19.43	[redacted]	[redacted]	–	[redacted]	–
Secukinumab	[redacted]	19.43	[redacted]	[redacted]	0.00	[redacted]	Secukinumab dominates

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.9 Sensitivity analyses

All sensitivity analyses were run from the primary analysis (biologic-naïve patients).

B.3.9.1 Probabilistic sensitivity analysis

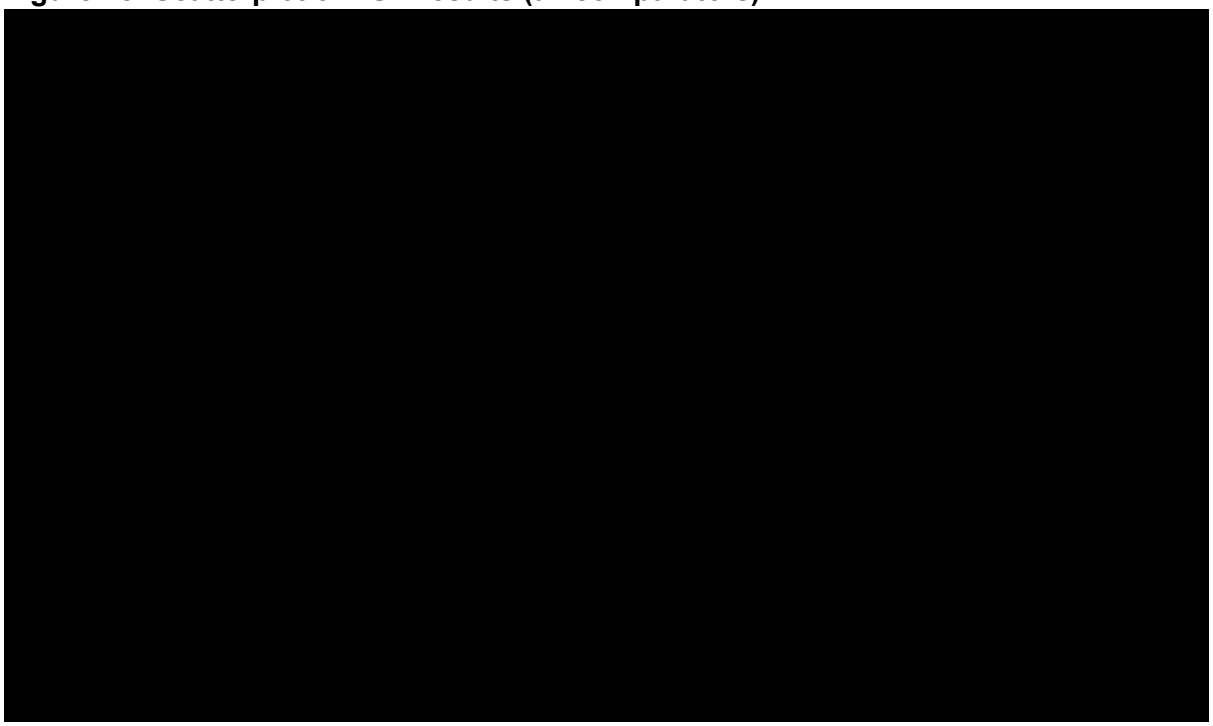
Joint parameter uncertainty was tested through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded. The results of probabilistic sensitivity analysis (Table 84) were found to be highly congruent with the base-case results (Table 82; Section B.3.7). Results were plotted on the cost-effectiveness plane (CEP; Figure 28 and Figure 29) and a multiple cost-effectiveness acceptability curve (CEAC; Figure 29) was generated.

Table 84: Results of probabilistic sensitivity analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER vs baseline (£/QALY)
CC	[redacted]	[redacted]	[redacted]	[redacted]	–
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	£7,388
Adalimumab biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£5,132
Etanercept biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	£18,404
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	£20,643
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	£18,129
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,208
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	£21,562

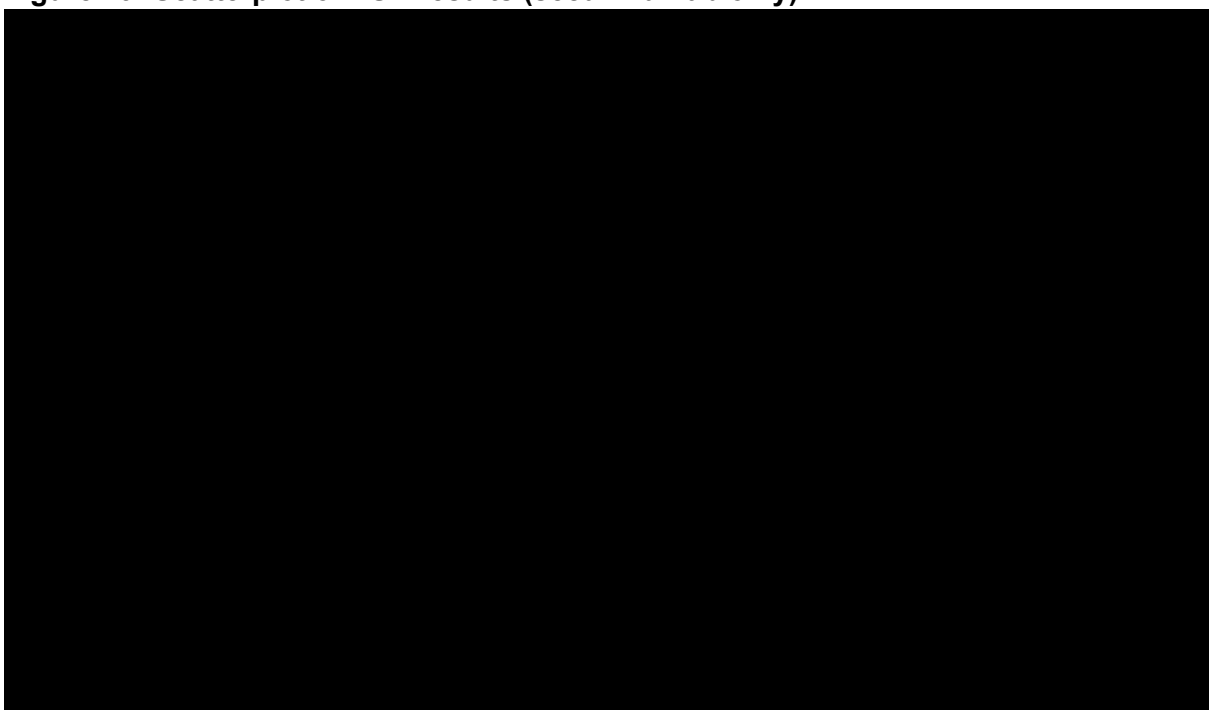
Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Figure 28: Scatterplot of PSA results (all comparators)



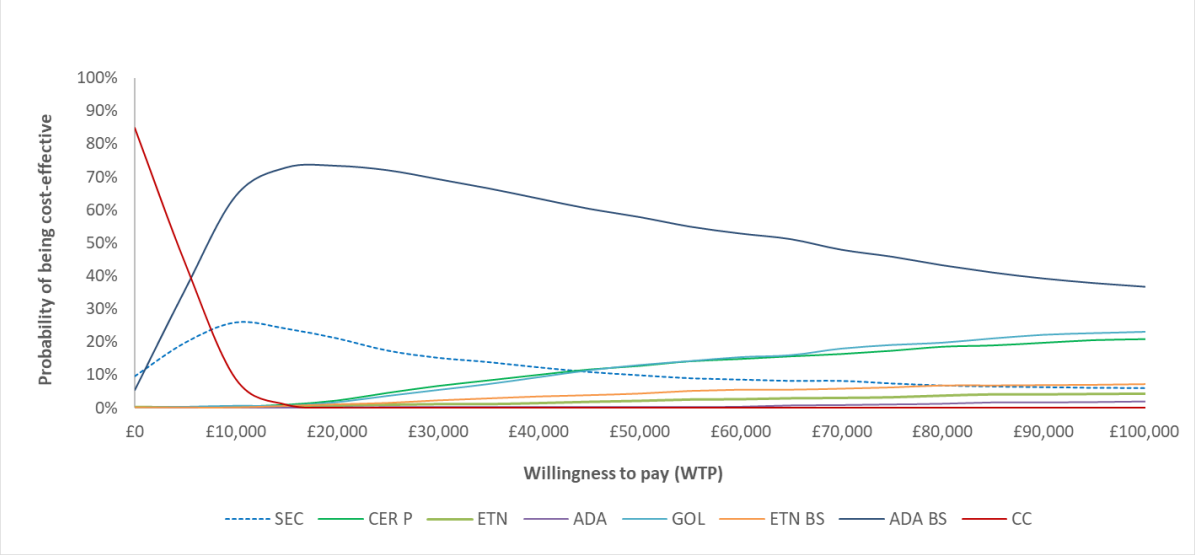
Abbreviations: ADA, adalimumab; ADA BS, adalimumab biosimilar; CC, conventional care; CER P, certolizumab pegol; ETN, etanercept; ETN BS, etanercept biosimilar; GOL, golimumab; QALY, quality-adjusted life-year; SEC, secukinumab.

Figure 29: Scatterplot of PSA results (secukinumab only)



Abbreviations: CC, conventional care; QALY, quality-adjusted life-year; SEC, secukinumab.

Figure 30: Multiple cost-effectiveness acceptability curve

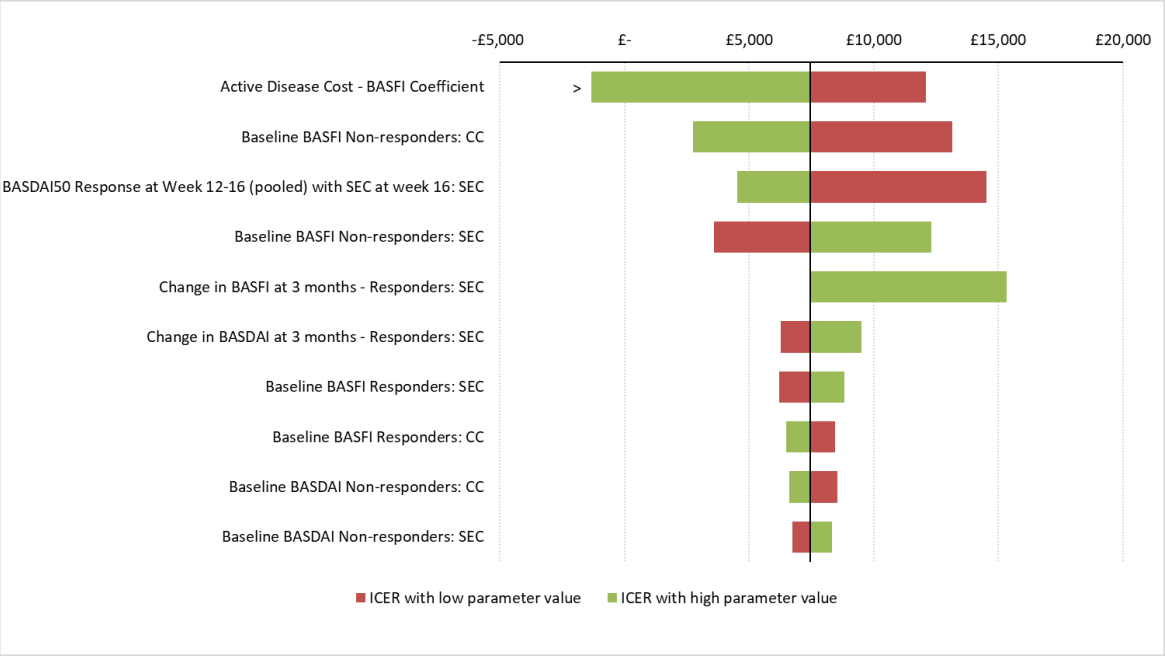


Abbreviations: ADA, adalimumab; ADA BS, adalimumab biosimilar; CC, conventional care; CER P, certolizumab pegol; ETN, etanercept; ETN BS, etanercept biosimilar; GOL, golimumab; SEC, secukinumab; WTP, willingness-to-pay.

B.3.9.2 Deterministic sensitivity analysis

Parameter uncertainty was tested using deterministic sensitivity analysis, in which all model parameters are systematically and independently varied over a plausible range determined by either the 95% CI, or ±10% where no estimates of precision were available. Upper and lower bounds used in deterministic sensitivity analysis are presented in Table 80. The results of deterministic sensitivity analysis are presented only for the comparison of secukinumab against CC (Figure 31).

Figure 31: Tornado diagram (secukinumab vs CC)



Abbreviations: BASDAI, Bath Ankylosing Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care; RR, rate ratio; SEC, secukinumab.

B.3.9.3 Scenario analysis

Scenario analyses were performed in which key structural assumptions were varied, and the results of each analysis reported. Considered scenarios and the results of each scenario are presented in Table 85.

Table 85: Scenario analyses performed

Area of uncertainty	Base case	Scenario	Relevant section of submission	Secukinumab ICER vs CC (£/QALY)	Fully incremental analysis (£/QALY)
***Base*-case**				***£7,459***	***Extendedly dominated***
Time horizon	Lifetime (maximum age of 100 years)	5 years	Section B.3.2.2	£14,228	Dominated
		10 years		£10,645	Dominated
		20 years		£8,726	Dominated
		40 years		£7,612	Extendedly dominated
Discounting	3.5% for costs and outcomes	No discounting	Section B.3.2.2	£5,494	Extendedly dominated
		3.5% for costs, 1.5% for outcomes		£6,027	Extendedly dominated
Measurement of response	BASDAI50	ASAS40†	Section B.3.2.2.1	£5,046	£5,046
Treatment sequencing	Excluded	Included	Section B.3.2.2.2	£1,914	£1,914
Impact on BASDAI and BASFI following discontinuation	Reverse initial gain	Revert to natural history	Section B.3.2.2.2	£8,229	Extendedly dominated
Biologic-specific treatment effect on BASFI	Treatment effect implemented from beginning of maintenance treatment	Treatment effect implemented after 4 years	Section B.3.2.2.2	£7,902	Extendedly dominated
		No treatment effect		£8,715	Extendedly dominated

Area of uncertainty	Base case	Scenario	Relevant section of submission	Secukinumab ICER vs CC (£/QALY)	Fully incremental analysis (£/QALY)
Timing of secukinumab response assessment	16 weeks	12 weeks	Section B.3.3.2	£5,881	Extendedly dominated
NMA	TNFα inhibitor exchangeable, Joint correlated BASDAI50, BASDAI change from baseline and BASFI change from baseline	Independent, uncorrelated	Section B.3.3.2	£7,936	£7,936
		Independent, Joint BASDAI50 and BASDAI change from baseline		£7,261	Extendedly dominated
		Independent, Joint correlated BASDAI50, BASDAI change from baseline and BASFI change from baseline		£7,347	Extendedly dominated
		All exchangeable, uncorrelated		£8,059	Extendedly dominated
		All exchangeable, Joint BASDAI50 and BASDAI change from baseline		£7,219	Extendedly dominated
		All exchangeable, Joint correlated BASDAI50, BASDAI change from baseline and BASFI change from baseline		£6,066	Extendedly dominated
		TNFα inhibitor exchangeable, uncorrelated		£7,981	Extendedly dominated
		TNFα inhibitor exchangeable, Joint BASDAI50 and BASDAI change from baseline		£7,235	Extendedly dominated
		Independent (Haibel excluded), uncorrelated		£8,142	£8,142
		Independent (Haibel excluded), Joint BASDAI50 and BASDAI change from baseline		£7,273	Extendedly dominated
		Independent (Haibel excluded), Joint correlated BASDAI50, BASDAI		£7,210	Extendedly dominated

Area of uncertainty	Base case	Scenario	Relevant section of submission	Secukinumab ICER vs CC (£/QALY)	Fully incremental analysis (£/QALY)
		change from baseline and BASFI change from baseline			
Utility model	Based on PREVENT	Model used by the assessment group for TA383	Section B.3.4	£7,545	Extendedly dominated
		Based on pooled PREVENT and MEASURE 1/2 data		£6,671	Extendedly dominated
		Model presented in McLeod et al		£7,632	Extendedly dominated
AE disutilities	Excluded	Included	Section B.3.4.4	£7,466	Extendedly dominated

† The base-case NMA model is not available for the ASAS40 outcome; this scenario was therefore run using the 'TNFα inhibitor exchangeable', uncorrelated NMA scenario.
Abbreviations: AE, adverse event; ASAS, Assessment of Spondyloarthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; QALY, quality-adjusted life year; TNFα, tumour necrosis factor alpha.

B.3.9.4 Summary of sensitivity analyses results

The results of the PSA were highly congruent with the results of the base-case analysis. Secukinumab was associated with the second highest probability of being cost-effective at conventional cost-effectiveness thresholds of £20,000 and £30,000 per QALY, after adalimumab biosimilar.

The most influential parameters identified in deterministic sensitivity analysis were those defining the relationship between BASFI and disease management costs, baseline BASFI in non-responders for both CC and secukinumab, and the response rate for secukinumab.

Most considered scenarios showed secukinumab to be associated with a similar ICER vs CC as in the base-case, and to be extendedly dominated by adalimumab biosimilar. However, in some scenarios, secukinumab was not extendedly dominated by adalimumab biosimilar: assuming ASAS40 response assessment, considering treatment sequencing, and several of the NMA scenarios.

B.3.9.5 Subgroup analysis

No subgroup analyses were performed. A secondary analysis was performed in the biologic-experienced population and is presented alongside the base-case (biologic-naïve patients) in Section B.3.7.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

The cost-effectiveness model has been verified by the model developers and by health economists not involved in the construction of the model. The model was verified using standard procedures:

- Cell-by-cell checks of logic and consistency
- Logical tests of model outputs.

Where possible, the results of the analysis were compared against previous NICE appraisals. A comparison of total costs and QALYs between TA383 and the current appraisal is presented in Table 86; this comparison was possible for CC, adalimumab, certolizumab pegol and etanercept. The results for the current

appraisal are shown to be relatively congruent with the results reported in the assessment group model for TA383. In both appraisals, the variation in cost for the modelled biologic therapies was small, and CC was associated with the lowest total costs and QALYs. Key differences between TA383 and the current appraisal are:

- Efficacy was assumed to be the same across all TNFα inhibitors in the cost-effectiveness analysis presented in TA383.
- Different utility models are used in TA383 and the current analysis; the model used in TA383 results in higher overall QALYs.

Table 86: Comparison between outcomes in NICE TA383 and current appraisal

Technology	Outcome	NICE TA383	Current appraisal
CC	Total costs	£89,493	[redacted]
	Total QALYs	9.96	[redacted]
Adalimumab	Total costs	£130,316	[redacted]
	Total QALYs	11.35	[redacted]
Certolizumab pegol	Total costs	£128,911	[redacted]
	Total QALYs	11.35	[redacted]
Etanercept	Total costs	£131,057	[redacted]
	Total QALYs	11.35	[redacted]

Abbreviations: QALY, quality-adjusted life-year.

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Relevance to patients with nr-axSpA

This analysis is expected to be broadly generalisable to clinical practice in England and Wales.

The base-case analysis does not include subsequent lines of biologic therapy, as no data are available on second or subsequent line use of TNFα inhibitors. This is consistent with the approach taken by the assessment group for TA383.

However, it is known that some patients in clinical practice will receive subsequent lines of biologic therapy; an exploratory scenario is therefore considered in which 100% of patients are assumed to receive a second-line biologic therapy. The results of this analysis are associated with a substantially improved ICER.

B.3.11.2 Strengths and limitations

Key strengths of the analysis are that:

- A broad range of NMA scenarios were considered, and the conclusions of the analysis were found to be robust to alternative assumptions.
- Wherever possible, the analysis was aligned with that presented by the assessment group for TA383.
- Cost-effectiveness in biologic-experienced patients was explored; this has not been possible in previous appraisals in nr-axSpA.
- A robust approach to estimating the relationship between BASDAI, BASFI and utility was taken, with a range of alternative model specifications considered, and EQ-5D data were used as per the NICE reference case.

Key limitations of the analysis are that:

- The NMA used to inform the cost-effectiveness model was associated with some limitations (Section B.2.9.6); in particular:
  - High placebo response rates compared with other included trials were observed in PREVENT for ASAS40, BASDAI change from baseline and BASFI change from baseline.
  - Baseline BASFI was observed to be higher in PREVENT compared with other included trials, and HLA-B27 was observed to be lower; together these may be expected to adversely affect results for secukinumab.
  - Data for golimumab were only available at 16 weeks but assumed to apply to the 12-week assessment point; however, the impact of this on the conclusions of the analysis is expected to be minimal.
- Baseline BASDAI/BASFI and change in BASDAI/BASFI from baseline conditional on response are not available for all comparators; in these cases, conditional values were estimated assuming the same ratio between non-responders and responders as observed for secukinumab patients in PREVENT.

B.3.11.3 Overall conclusions

The results of the primary analysis (biologic-naïve patients) showed secukinumab to be the biologic associated with the lowest overall costs. Only adalimumab biosimilar was associated with a lower ICER vs CC than secukinumab; however, the results

were similar (£5,445 and £7,459 per QALY, respectively). It should be noted that the price applied for adalimumab biosimilar is the interim national reference price set by the NHS England tendering process (98), which is only valid for the financial year 2019/20; when the lowest available list price is assumed for adalimumab biosimilar, it is found to be extendedly dominated, with secukinumab having the only ICER below £20,000 per QALY.

It is also noted that a number of currently recommended biologics (etanercept, certolizumab pegol, golimumab) are associated with ICERs above £30,000 per QALY when compared with secukinumab.

In the secondary analysis (biologic-experienced patients), secukinumab is found to be dominant compared with CC, with [redacted]. Secukinumab is the only product to have been compared with CC in biologic-experienced patients in a NICE technology appraisal.

In both TA383 and TA497, the recommendations issued by NICE included statements that if more than one treatment is considered suitable by patients and their clinicians, the least expensive (taking into account administration costs and patient access schemes) should be chosen. Adopting similar wording for guidance on secukinumab would ensure that the best value biologic is used in clinical practice. An additional option with an alternative mechanism of action is expected to be of value to patients.

The results of this analysis are relatively congruent with those presented by the assessment group for TA383. Extensive sensitivity analyses were performed, and results were found to be similar to those of the base-case analysis.

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B.5 Appendices

All appendices are provided as separate documents:

- Appendix C: Draft summary of product characteristics (SmPC)
- Appendix D: Identification, selection and synthesis of clinical evidence
- Appendix E: Summary of subgroup analyses
- Appendix F: Adverse reactions
- Appendix G: Published cost-effectiveness studies
- Appendix H: Health-related quality-of-life studies
- Appendix I: Cost and healthcare resource identification, measurement and valuation
- Appendix J: Clinical outcomes and disaggregated results from the model
- Appendix K: Checklist of confidential information
- Appendix L: Alternative NMA models

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Secukinumab for treating non-radiographic axial spondyloarthritis [ID1419]

Clarification questions

January 2020

File name	Version	Contains confidential information	Date
	1	Yes ([redacted] and [redacted])	28/01/20

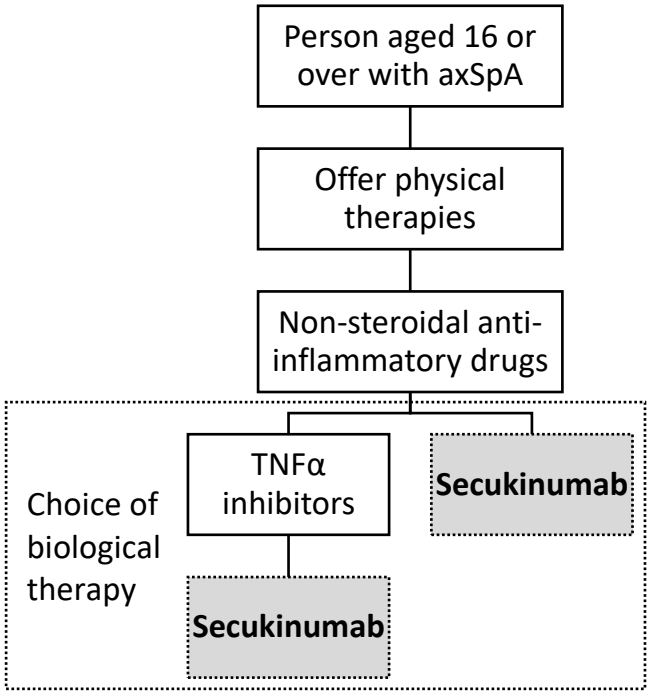
Section A: Clarification on effectiveness data

General issues

A1. In the marketing indication [page 15 of company submission (CS)] secukinumab is indicated for patients "who have responded inadequately to conventional therapy" in AS but for patients "who have "responded inadequately to… NSAIDs" for nr-axSpA. What is the reason for this slight discrepancy?

Response: For patients with AS, conventional therapy includes both NSAIDs and physiotherapy (as defined in TA383 [1] and TA407 [2]). For patients with nr-axSpA, the licence application has been submitted to the EMA for approval for use after NSAIDs (as shown in Figure 1, and Figure 4 of the CS). As presented in the CS, the pathway of care shows that physiotherapy is followed by NSAIDs (Figure 1), therefore the wording difference has no meaningful implication for the positioning of secukinumab.

Figure 1: NICE guideline for managing spondyloarthritis (including proposed positioning of secukinumab)



Abbreviations: axSpA, axial spondyloarthritis; TNFα, tumour necrosis factor alpha.

A2. The method of administration for the recommended dose is 150mg at weeks 0, 1, 2, 3, and 4 (i.e. the “Loading” dose, page 15 of CS). Does this mean recommended by the company, or some other agency?

Response: This is the recommended dosing for treatment of AS and the anticipated EMA recommendation for nr-axSpA.

PREVENT trial - general

A3. The population for PREVENT [Table 5, page 31 of CS] is defined as patients meeting ASAS criteria PLUS abnormal CRP or MRI. Can you please explain why ASAS criteria alone were not used (and hence why people negative on both CRP and MRI were excluded)?

Response: This definition is aligned with the current licensed population of all bDMARDs in Europe and as requested by the FDA and EMA.

A4. Was the open label “escape treatment” of 150mg secukinumab used for all non-responders, regardless of which arm they were randomised to? Was transfer to this open label group based on ASAS40 response, or other response outcomes? Please confirm that blinding to treatment before 20 weeks was not broken for patients transferred to the open label arm.

Response: Yes, to ensure blinding of the study, the open label escape treatment of 150 mg secukinumab was used for all non-responders regardless of their original randomisation group. The response was based on the clinical judgement[a] of disease activity by the investigator and the patient to reflect the real-world setting. Therefore, no response criteria were requested for the escape. The original randomised treatment assignment (secukinumab 150 mg or placebo) remained blinded for at least 20 weeks.

A5. The ERG notes some unusual values and variation in baseline characteristics [Table 9, page 41 of CS]. Could the company comment on why baseline hsCRP, and

[a] nr-axSpA is a multifaceted disease and the assessment of responder status should be based on the global clinical picture and not on a single efficacy parameter; repeatedly [e.g. at two or more consecutive visits] not achieving a clinically meaningful improvement in the BASDAI of ≥20% or ≥1 unit [0–10 scale] [3] may be considered as a general guidance for considering a patient inadequate responder to study treatment.

HLA-B27 proportions varied (particularly between “load” and “no load” arms)? Many mean values (e.g BASDI, BASFI) are higher than might be expected for UK patients eligible for secukinumab. Could the company comment on why this might be? Where baseline distributions are skewed (e.g. time since diagnosis, hsCRP) could the company provide median values and interquartile ranges at baseline?

Response: Patients were stratified at randomisation according to which subgroup of objective signs of inflammation they belonged to, and not any other criteria. The differences observed in mean values between arms for time since diagnosis and hsCRP are mainly driven by outliers with high values; median values are comparable (Table 1).

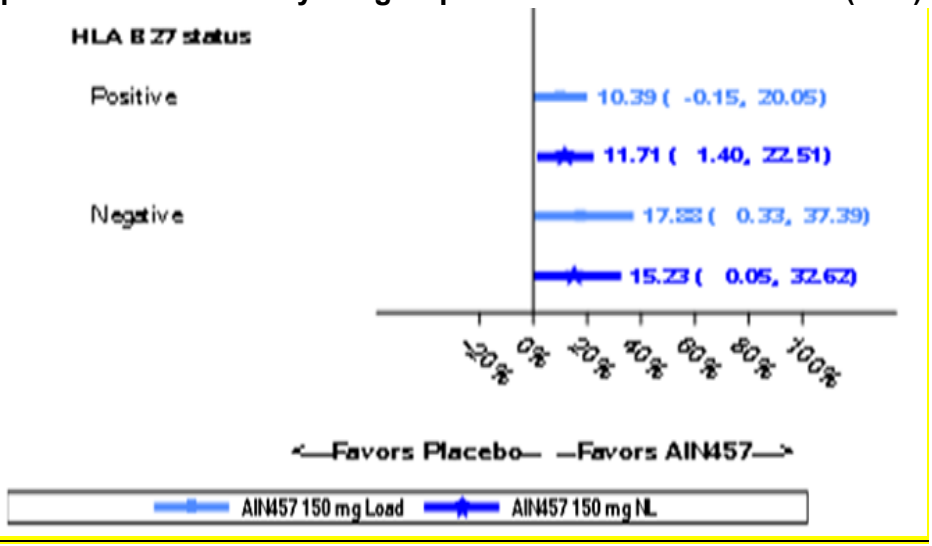
Table 1: Selected baseline characteristics (randomised set)

	Secukinumab 150 mg Load (N=185)	Secukinumab 150 mg No Load (N=184)	Placebo (N=186)	Total (N=555)
hsCRP(mg/L)				
Mean	13.17	9.67	10.76	11.20
SD	27.209	15.815	21.335	21.969
Minimum	[redacted]	[redacted]	[redacted]	[redacted]
Q1	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q3	[redacted]	[redacted]	[redacted]	[redacted]
Maximum	[redacted]	[redacted]	[redacted]	[redacted]
Time since first diagnosis of axSpA (years)				
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Minimum	[redacted]	[redacted]	[redacted]	[redacted]
Q1	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Q3	[redacted]	[redacted]	[redacted]	[redacted]
Maximum	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: axSpA, axial spondyloarthritis; hsCRP, high-sensitivity c-reactive protein.

The differences observed in mean values between arms for HLA-B27 arose by chance. However, there is no evidence to suggest that response differed based on HLA-B27 status in PREVENT (Figure 2). Therefore, this baseline difference was not considered relevant for the results of the study.

Figure 2: Forest plot for the difference of ASAS40 response between secukinumab and placebo at Week 16 by subgroups based on HLA-B27 status (FAS)

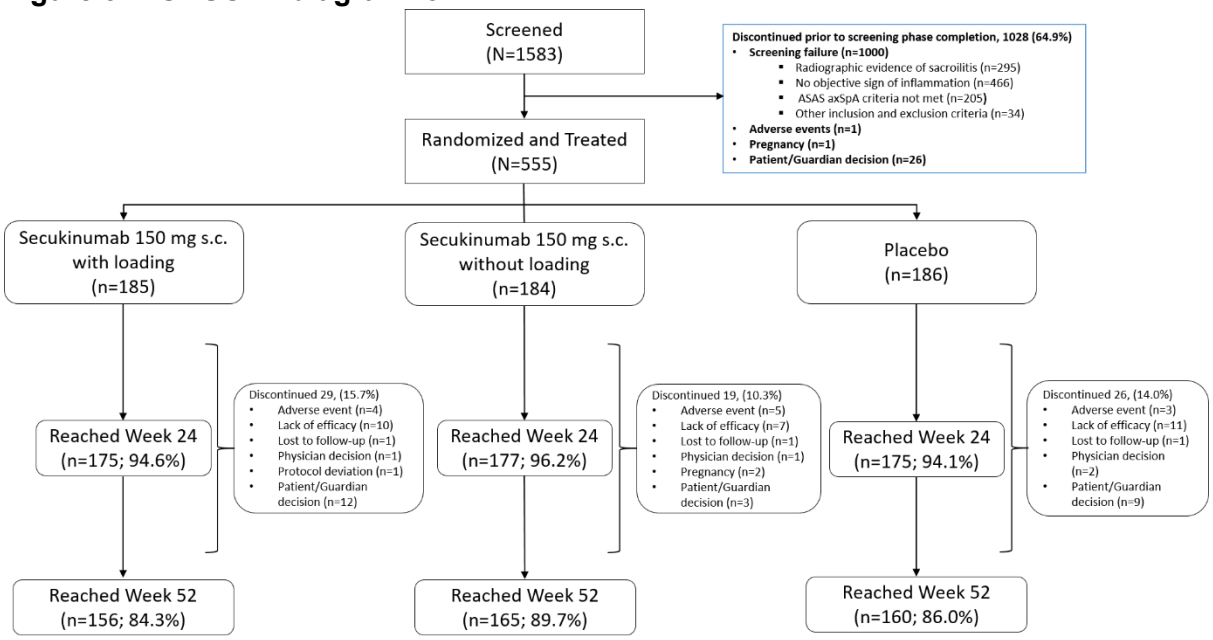


Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; FAS, full analysis set; HLA, human leukocyte antigen.

A6. Please present a CONSORT diagram for the PREVENT trial with the same level of detail as presented for the C-AxSpAnd trial in Appendix D.2.3. This should include a breakdown of specific reasons for not being randomised for the n=1028 patients. Please provide patient flow data up to week 52 and include numbers and details about use of escape treatments.

Response: A consort diagram for the PREVENT trial is presented in Figure 3. The PREVENT trial is currently ongoing. Our submission presented the Week 16 results as the primary analysis, using data from an interim database lock when all patients had completed 24 weeks of the trial, as well as interim Week 52 analysis.

Figure 3: CONSORT diagram for PREVENT



A7. Please provide all update search strategies for the clinical systematic literature review carried out on 16th September 2019. (Section D.1, Appendix D page1)

Response: Please see Table 2 to Table 7 below for the search strategies for the nr-axSpA and AS+nr-axSpA update carried out on 16th September 2019.

Table 2: Search strategy update for nr-axSpA: Embase and MEDLINE via Embase.com (16/09/19)

Parameter	#	Search String	Yield
Disease	1.	'spondylarthritis'/exp OR (((nonradiographic OR 'non radiographic' OR 'non-radiographic') NEAR/6 (spondyl* OR spa)):ab,ti) OR ((axial NEAR/6 (spondyl* OR spa)):ab,ti) OR 'nr axspa':ab,ti OR axspa:ab,ti	8559
Treatment	2.	'etanercept'/exp OR etanercept OR benepali OR embrel OR enbrel OR erelzi OR 'etanercept szzs' OR 'etanercept-szzs' OR lifmior OR 'tnr 001' OR tnr001	30880
	3.	'adalimumab'/exp OR adalimumab OR 'abp 501' OR abp501 OR 'adalimumab atto' OR 'adalimumab-atto' OR amgevita OR amjevita OR humira OR imraldi OR 'monoclonal antibody d2e7' OR solymbic OR trudexa	31945
	4.	'certolizumab pegol'/exp OR 'certolizumab pegol' OR 'cdp 870' OR cdp870 OR 'cimzia' OR 'pha 738144' OR pha738144	6178
	5.	'golimumab'/exp OR golimumab OR 'cnto 148' OR cnto148 OR simponi OR 'simponi aria'	6466
	6.	'ixekizumab'/exp OR ixekizumab OR 'ly 2439821' OR ly2439821 OR taltz	1464
	7.	'secukinumab'/exp OR secukinumab OR 'ain 457' OR 'ain457' OR Cosentyx	3082
	8.	2 OR 3 OR 4 OR 5 OR 6 OR 7	52156
	9.	1 AND 8	1642

Parameter	#	Search String	Yield
Disease + Treatment	10.	'letter'/de OR 'review'/de OR commentary OR 'editorial'/de	4133565
	11.	9 NOT 10	1297
	12.	'animal experiment'/exp OR 'experimental animal'/exp OR 'rodent'/exp OR 'animal'/de OR 'not human' OR 'nonhuman'/de OR 'animal model'/de OR rat:ti OR rats:ti OR mouse:ti OR mice:ti	8759062
	13	11 NOT 12 AND [english]/lim AND [28-2-2019]/sd	192

Table 3: Search strategy update for nr-axSpA: MEDLINE In Process via Ovid (16/09/19)

Parameter	#	Search String	Yield
Disease	1.	exp spondylarthritis/ or (axial adj6 (spondyl* or spa)).ti,ab. or ((nonradiographic or 'non radiographic' or non-radiographic) adj6 spondyl* or spa).ti,ab. or ('nr-axSpA' or axspa).ti,ab	1579
Treatment	2.	exp etanercept/ or (etanercept or benepali or embrel or enbrel or erelzi or 'etanercept szzs' or 'etanercept-szzs' or lifmior or 'tnr 001' or tnr001).mp.	7508
	3.	exp adalimumab/ or (adalimumab or 'abp 501' or abp501 or 'adalimumab atto' or 'adalimumab-atto' or amgevita or amjevita or humira or imraldi or 'monoclonal antibody d2e7' or solymbic or trudexa).mp.	7510
	4.	exp certolizumab pegol/ or ('certolizumab pegol' or 'cdp 870' or cdp870 or 'cimzia' or 'pha 738144' or pha738144).mp.	893
	5.	exp golimumab/ or (golimumab or 'cnto 148' or cnto148 or simponi or 'simponi aria').mp.	1083
	6.	exp ixekizumab/ or (ixekizumab or 'ly 2439821' or ly2439821 or taltz).mp.	435
	7.	exp secukinumab/ or (secukinumab or 'ain 457' or 'ain457' or cosentyx).mp.	893
	8.	2 OR 3 OR 4 OR 5 OR 6 OR 7	13863
Disease + Treatment	9.	1 AND 8	220
	10.	Limit 9 to english language	216
	11	Limit 10 to ed=20190228-20190916	10

Table 4: Search strategy update for nr-axSpA: Cochrane via Ovid (16/09/19)

Parameter	#	Search String	Yield
Disease	1.	exp 'spondylarthritis'/ or (axial adj6 (spondyl* or spa)).ti,ab. or ((nonradiographic or 'non radiographic' or non-radiographic) adj6 spondyl* or spa).ti,ab. or ('nr-axSpA' or axspa).ti,ab.	611
Treatment	2.	exp 'etanercept'/ or (etanercept or benepali or embrel or enbrel or erelzi or 'etanercept szzs' or 'etanercept-szzs' or lifmior or 'tnr 001' or tnr001).mp.	2120
	3.	exp 'adalimumab'/ or (adalimumab or 'abp 501' or abp501 or 'adalimumab atto' or 'adalimumab-atto' or amgevita or amjevita or humira or imraldi or 'monoclonal antibody d2e7' or solymbic or trudexa).mp.	2656
	4.	exp 'certolizumab pegol'/ or ('certolizumab pegol' or 'cdp 870' or cdp870 or 'cimzia' or 'pha 738144' or pha738144).mp.	501
	5.	exp 'golimumab'/ or (golimumab or 'cnto 148' or cnto148 or simponi or 'simponi aria').mp.	583
	6.	exp 'ixekizumab'/ or (ixekizumab or 'ly 2439821' or ly2439821 or taltz).mp.	355
	7.	exp 'secukinumab'/ or (secukinumab or 'ain 457' or 'ain457' or cosentyx).mp.	637
	8.	2 OR 3 OR 4 OR 5 OR 6 OR 7	5830
Disease + Treatment	9.	1 AND 8	212
	10.	Limit 9 to English language	193
	11.	Deduplicate 10	179
	12	limit 11 to yr="2019"	4

Table 5: Search strategy update for AS+nr-axSpA: Embase and MEDLINE via Embase.com (16/09/19)

Parameter	#	Search String	Yield
Disease	1.	'spondylarthritis'/exp OR 'ankylosing spondylitis'/exp OR (((ankyl* OR axial) NEAR/2 (spine* OR spinal OR vertebra*)):ab,ti) OR (((nonradiographic OR 'non radiographic' OR 'non-radiographic') NEAR/6 (spondyl* OR spa)):ab,ti) OR ((axial NEAR/6 (spondyl* OR spa)):ab,ti) OR 'nr axspa':ab,ti OR axspa:ab,ti	37090
Treatment	2.	'etanercept'/exp OR etanercept OR benepali OR embrel OR enbrel OR erelzi OR 'etanercept szzs' OR 'etanercept-szzs' OR lifmior OR 'tnr 001' OR tnr001	30880
	3.	'adalimumab'/exp OR adalimumab OR 'abp 501' OR abp501 OR 'adalimumab atto' OR 'adalimumab-atto' OR amgevita OR amjevita OR humira OR imraldi OR 'monoclonal antibody d2e7' OR solymbic OR trudexa	31945
	4.	'certolizumab pegol'/exp OR 'certolizumab pegol' OR 'cdp 870' OR cdp870 OR 'cimzia' OR 'pha 738144' OR pha738144	6178
	5.	'golimumab'/exp OR golimumab OR 'cnto 148' OR cnto148 OR simponi OR 'simponi aria'	6466
	6.	'ixekizumab'/exp OR ixekizumab OR 'ly 2439821' OR ly2439821 OR taltz	1464
	7.	'secukinumab'/exp OR secukinumab OR 'ain 457' OR 'ain457' OR Cosentyx	3082
	8.	2 OR 3 OR 4 OR 5 OR 6 OR 7	52156
Disease + Treatment	9.	1 AND 8	6104
	10.	'letter'/de OR 'review'/de OR commentary OR 'editorial'/de	4133565
	11.	9 NOT 10	4471
	12.	'animal experiment'/exp OR 'experimental animal'/exp OR 'rodent'/exp OR 'animal'/de OR 'not human' OR 'nonhuman'/de OR 'animal model'/de OR rat:ti OR rats:ti OR mouse:ti OR mice:ti	8759062
	13	11 NOT 12 AND [english]/lim	4019
	14	13 NOT 'conference abstract'/it	1947
	15	14 AND 'conference abstract'/it AND [2016-2019]/py	1001
	16	14 OR 15	2948
	16	14 OR 15 AND [6-5-2019]/sd	391

Table 6: Search strategy update for AS+nr-axSpA: MEDLINE In Process via Ovid (16/09/19)

Parameter	#	Search String	Yield
Disease	1.	exp spondylarthritis/or exp ankylosing spondylitis/ or ((ankyl$ or axial) adj2 spondyl$).ti,ab. Or (ankyl$ adj2 (spine$ or spinal or vertbra$)).ti,ab. or (axial adj6 (spondyl* or spa)).ti,ab. or ((nonradiographic or 'non radiographic' or non-radiographic) adj6 spondyl* or spa).ti,ab. or ('nr-axSpA' or axspa).ti,ab	22023
Treatment	2.	exp etanercept/ or (etanercept or benepali or embrel or enbrel or erelzi or 'etanercept szzs' or 'etanercept-szzs' or lifmior or 'tnr 001' or tnr001).mp.	7508
	3.	exp adalimumab/ or (adalimumab or 'abp 501' or abp501 or 'adalimumab atto' or 'adalimumab-atto' or amgevita or amjevita or humira or imraldi or 'monoclonal antibody d2e7' or solymbic or trudexa).mp.	7510
	4.	exp certolizumab pegol/ or ('certolizumab pegol' or 'cdp 870' or cdp870 or 'cimzia' or 'pha 738144' or pha738144).mp.	893
	5.	exp golimumab/ or (golimumab or 'cnto 148' or cnto148 or simponi or 'simponi aria').mp.	1083
	6.	exp ixekizumab/ or (ixekizumab or 'ly 2439821' or ly2439821 or taltz).mp.	435
	7.	exp secukinumab/ or (secukinumab or 'ain 457' or 'ain457' or cosentyx).mp.	893
	8.	2 OR 3 OR 4 OR 5 OR 6 OR 7	13863
Disease + Treatment	9.	1 AND 8	2202
	10.	Limit 9 to english language	2065
	11	Limit 10 to ed=20190228-20190916	95

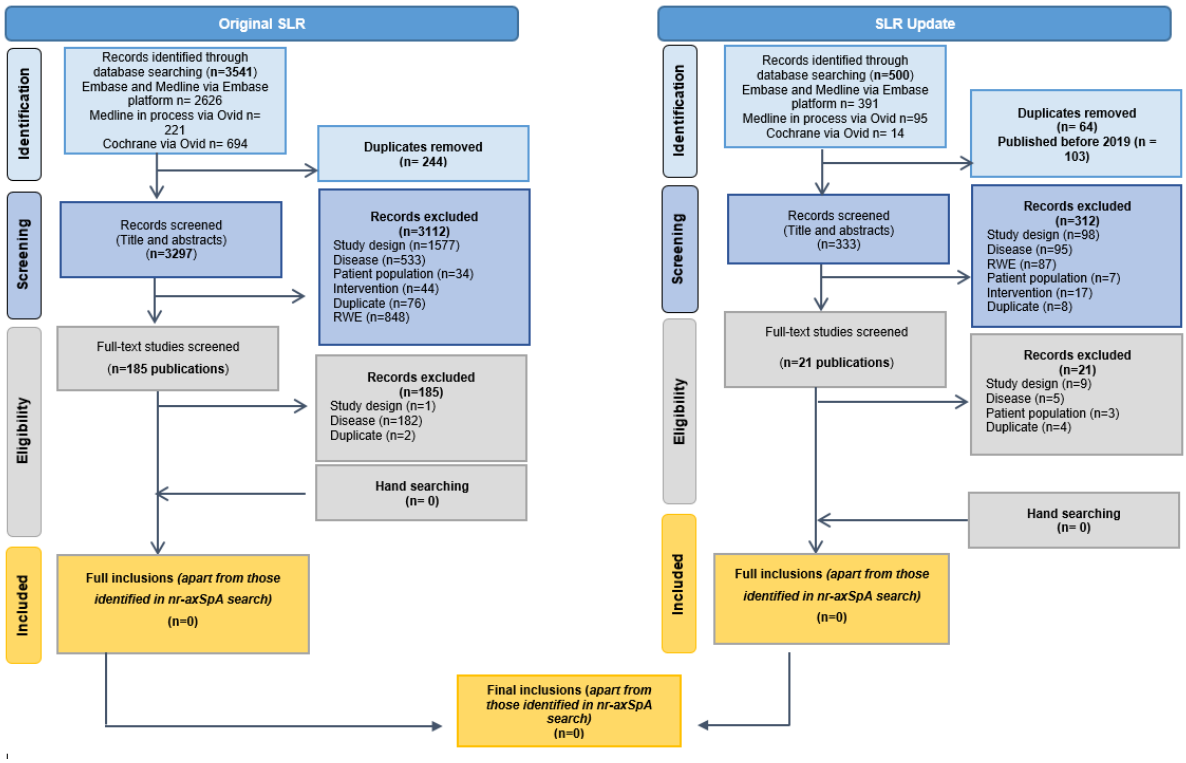
Table 7: Search strategy update for AS+nr-axSpA: Cochrane via Ovid (16/09/19)

Parameter	#	Search String	Yield
Disease	1.	exp 'spondylarthritis'/ or exp ankylosing spondylitis/ or ((ankyl$ or axial) adj2 spondyl$).ti.ab or (ankyl$ adj2 (spine$ or spinal or vertebra$)).ti,ab. Or (axial adj6 (spondyl* or spa)).ti,ab. or ((nonradiographic or 'non radiographic' or non-radiographic) adj6 spondyl* or spa).ti,ab. or ('nr-axSpA' or axspa).ti,ab.	2250
Treatment	2.	exp 'etanercept'/ or (etanercept or benepali or embrel or enbrel or erelzi or 'etanercept szzs' or 'etanercept-szzs' or lifmior or 'tnr 001' or tnr001).mp.	2120
	3.	exp 'adalimumab'/ or (adalimumab or 'abp 501' or abp501 or 'adalimumab atto' or 'adalimumab-atto' or amgevita or amjevita or humira or imraldi or 'monoclonal antibody d2e7' or solymbic or trudexa).mp.	2656
	4.	exp 'certolizumab pegol'/ or ('certolizumab pegol' or 'cdp 870' or cdp870 or 'cimzia' or 'pha 738144' or pha738144).mp.	501
	5.	exp 'golimumab'/ or (golimumab or 'cnto 148' or cnto148 or simponi or 'simponi aria').mp.	583
	6.	exp 'ixekizumab'/ or (ixekizumab or 'ly 2439821' or ly2439821 or taltz).mp.	355
	7.	exp 'secukinumab'/ or (secukinumab or 'ain 457' or 'ain457' or cosentyx).mp.	637
	8.	2 OR 3 OR 4 OR 5 OR 6 OR 7	5830
Disease + Treatment	9.	1 AND 8	982
	10.	Limit 9 to English language	787
	11.	Deduplicate 10	698
	12	limit 11 to yr="2019"	14

A8. The number of records identified from MEDLINE in process and the Cochrane Library reported in the first box of the PRISMA flow diagram for the AS search (Original SLR, Figure 2, Appendix D, page 10) differ from those reported in the search strategies shown in Table 6 MEDLINE in process (Appendix D, page5) and in Table 7 Cochrane (Appendix D, page 6). Please could this be checked and corrected.

Response: The numbers reported in the table are correct, but they have been inadvertently swapped in the PRISMA diagram – the diagram should show 221 records for Medline and 694 records for Ovid. A corrected diagram is presented in Figure 4.

Figure 4: Original SLR: PRISMA flow for (AS+nr-axSpA) screening



PREVENT trial – statistical methods

A9. PRIORITY. CS Section B.2.4.2.5 implies that patients who dropped out or who had no data at a time point were treated as non-responders, but for continuous outcomes "non-responder imputation" was used to create outcomes. However, all results [e.g. CS Table 14 and Figure 7] are described as using "non-responder imputation" even for binary outcomes. Could the company please explain exactly how imputation was used, and how this varied across outcomes?

Response: As explained in CS Section B.2.4.2.5, non-responder imputation (NRI) was used for binary efficacy variables, and a mixed-effects model repeated measures (MMRM) was used for continuous variables. The exception to this was SI joint oedema on MRI, which was analysed using analysis of covariance (ANCOVA) based on multiple imputation (MI) under the missing at random (MAR) assumption. The heading of each results table/figure in the CS includes a description of the method for dealing with missing data (NRI for binary outcomes and MMRM/ANCOVA for continuous outcomes, as detailed above). Full details are provided in Section 17.2.3 of the statistical analysis plan (SAP) [4].

A10. To support question A9, please provide more statistical detail on the MMRM imputation models used, including whether this was single or multiple imputation, the exact parameters used for imputation, and how confidence intervals were adjusted for imputation. Please provide relevant citations to support this method.

Response: A linear regression model was used to perform MI under an MAR assumption. To help preserve the relationship between outcome and covariates within each treatment a separate model was run for each treatment. This also helped to ensure that the imputation model did not make stronger assumptions on data relations than the analysis model. Full details are provided in Section 17.2.3 of the SAP [4].

A11. The ERG finds the description of the sequential hypothesis testing procedure [CS section B.2.4.2.3] to be unclear. Please provide further detail on how this procedure was performed (for example, what happened if hypotheses were NOT rejected). Please also provide relevant citations to justify this approach.

Response: All null hypotheses were rejected, however if any had not been rejected there would be no further testing for the remaining hypotheses in the sequence. Please see Section 11.5 of the SAP for details of the sequential hypothesis testing procedure [4].

A12. The CS does not describe how analyses of continuous outcomes were performed. Were they linear regressions of change from baseline against treatment used, or full ANCOVA models of outcome regressed against baseline and treatment? Please provide a full statistical specification for the continuous outcome models.

Response: Some endpoints were analysed using ANCOVA models, which included factors and covariates as specified for respective analysis. Least square mean (LSM) estimates for each treatment group and LSM difference, confidence intervals and p-value for the difference between each dose of secukinumab and placebo, and between secukinumab doses if relevant, were calculated.

Other endpoints were analysed using a longitudinal model that comprises several visits. MMRM models were used with factors, covariates, interactions and covariance structure as specified for respective analysis. Least-square-mean (LSM) estimates

for each treatment group and LSM difference, confidence intervals and p-value for the difference between each dose of secukinumab and placebo, and between secukinumab doses if relevant, were calculated at appropriate analysis visits.

Full details are provided in the SAP [4].

PREVENT trial – data and results

A13. PRIORITY. To address the issues raised in question A9, could the company provide the following data for the analysis *at 16 weeks:*

For each analysed outcome and each trial arm:

- Number of patients with and without an observed outcome (i.e. with/without sufficient data to estimate outcome)
- [For binary outcomes] Number of observed events/responses (without imputation)
- [For continuous outcomes] Mean difference from baseline, with its SD, excluding patients with imputed results.

Response: The data requested is provided in Table 8 (primary endpoint), Table 9 to Table 20 (secondary endpoints), Table 21 to Table 25 (HRQoL endpoints), and Table 26 (exploratory endpoints).

Note that in Table 26, observed data for individual BASMI components are presented in lieu of observed data for BASMI linear change from baseline which is not available.

Table 8: Primary endpoint: ASAS40 response in TNFα-naïve patients using observed data, Week 16, FAS

Treatment group	n/M (%)	95% CI
Secukinumab 150 mg Load (N=164)	68/155 (43.9)	[redacted]
Secukinumab 150 mg No Load (N=166)	70/158 (44.3)	[redacted]
Placebo (N=171)	50/165 (30.3)	[redacted]

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; TNFα, tumour necrosis factor alpha.

Table 9: Secondary endpoint: ASAS40 response in all patients using observed data, Week 16, FAS

Treatment group	n/M (%)	95% CI
Secukinumab 150 mg Load (N=185)	74/175 (42.3)	[redacted]
Secukinumab 150 mg No Load (N=184)	75/176 (42.6)	[redacted]
Placebo (N=186)	52/177 (29.4)	[redacted]

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group.

Table 10: Secondary endpoint: ASAS 5/6 response in all patients using observed data, Week 16, FAS

Treatment group	n/M (%)	95% CI
Secukinumab 150 mg Load (N=185)	74/181 (40.9)	[redacted]
Secukinumab 150 mg No Load (N=184)	66/177 (37.3)	[redacted]
Placebo (N=186)	44/176 (25.0)	[redacted]

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group.

Table 11: Secondary endpoint: BASDAI change from baseline in all patients using observed data, Week 16, FAS

Treatment group	n	Mean change (SD)
Secukinumab 150 mg Load (N=185)	181	–2.703 (2.6523)
Secukinumab 150 mg No Load (N=184)	177	–2.702 (2.4640)
Placebo (N=186)	177	–1.778 (2.2675)

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; FAS, full analysis set; n, number of patients with measures at both baseline and the corresponding post baseline visit; N, the number of patients in each treatment group of the specified analysis set; SD, standard deviation.

Table 12: Secondary endpoint: BASDAI50 response in all patients using observed data, Week 16, FAS

Treatment group	n/M (%)	95% CI
Secukinumab 150 mg Load (N=185)	69/181 (38.1)	[redacted]
Secukinumab 150 mg No Load (N=184)	69/177 (39.0)	[redacted]
Placebo (N=186)	39/177 (22.0)	[redacted]

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group.

Table 13: Secondary endpoint: hsCRP change from baseline in all patients using observed data, Week 16, FAS

Treatment group	n	Mean change (SD)
Secukinumab 150 mg Load (N=185)	180	–7.90 (26.168)
Secukinumab 150 mg No Load (N=184)	176	–4.67 (14.954)
Placebo (N=186)	175	–2.42 (14.833)

Abbreviations: FAS, full analysis set; hsCRP, high-sensitivity c-reactive protein; n, number of patients with measurements at both baseline and the post-baseline visit; N, number of patients in the randomised treatment group; SD, standard deviation.

Table 14: Secondary endpoint: BASFI change from baseline in all patients using observed data, Week 16, FAS

Treatment group	n	Mean change (SD)
Secukinumab 150 mg Load (N=185)	181	–2.234 (2.8925)
Secukinumab 150 mg No Load (N=184)	177	–1.967 (2.4894)
Placebo (N=186)	177	–1.421 (2.3345)

Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index; FAS, full analysis set; n, number of patients with measures at both baseline and the corresponding post baseline visit; N, number of patients in each treatment group of the specified analysis; SD, standard deviation.

Table 15: Secondary endpoint: MRI SI joint oedema score change from baseline in all patients using observed data, Week 16, FAS

Treatment group	n	Mean change (SD)
Secukinumab 150 mg Load (N=185)	180	–1.73 (3.241)
Secukinumab 150 mg No Load (N=184)	177	–1.06 (2.523)
Placebo (N=186)	174	–0.45 (2.077)

Abbreviations: FAS, full analysis set; MRI, magnetic resonance imaging; n, number of patients with measures at both baseline and the corresponding post baseline visit; N, number of patients in each treatment group of the specified analysis set; SD, standard deviation; SI sacroiliac.

Table 16: Secondary endpoint: ASAS20 response in all patients using observed data, Week 16, FAS

Treatment group	n/M (%)	95% CI
Secukinumab 150 mg Load (N=185)	105/175 (60.0)	[redacted]
Secukinumab 150 mg No Load (N=184)	107/176 (60.8)	[redacted]
Placebo (N=186)	85/177 (48.0)	[redacted]

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group.

Table 17: Secondary endpoint: SF-36 PCS change from baseline in all patients using observed data, Week 16, FAS

Treatment group	n	Mean change (SD)
Secukinumab 150 mg Load (N=185)	182	7.053 (9.0568)
Secukinumab 150 mg No Load (N=184)	176	6.650 (7.9087)
Placebo (N=186)	178	4.103 (6.6912)

Abbreviations: FAS, full analysis set; n, number of patients with measures at both baseline and the corresponding post baseline visit; N, number of patients in each treatment group of the specified analysis set; PCS, physical component summary; SD, standard deviation; SF-36, short form-36.

Table 18: Secondary endpoint: SF-36 MCS change from baseline in all patients using observed data, Week 16, FAS

Treatment group	n	Mean change (SD)
Secukinumab 150 mg Load (N=185)	182	[redacted]
Secukinumab 150 mg No Load (N=184)	176	[redacted]
Placebo (N=186)	178	[redacted]

Abbreviations: FAS, full analysis set; MCS, mental component summary; n, number of subjects with measures at both baseline and the corresponding post baseline visit; N, number of subjects in each treatment group of the specified analysis set; SD, standard deviation; SF-36, short form-36.

Table 19: Secondary endpoint: ASQoL change from baseline in all patients using observed data, Week 16, FAS

Treatment group	n	Mean change (SD)
Secukinumab 150 mg Load (N=185)	181	–4.523 (4.9041)
Secukinumab 150 mg No Load (N=184)	176	–4.503 (4.8262)
Placebo (N=186)	177	–2.761 (4.4763)

Abbreviations: ASQoL, Ankylosing Spondylitis Quality of Life; FAS, full analysis set; n, number of subjects with measures at both baseline and the corresponding post baseline visit; N, number of subjects in each treatment group of the specified analysis set; SD, standard deviation.

Table 20: Secondary endpoint: ASAS partial remission in all patients using observed data, Week 16, FAS

Treatment group	n/M (%)	95% CI
Secukinumab 150 mg Load (N=185)	40/178 (22.5)	[redacted]
Secukinumab 150 mg No Load (N=184)	39/177 (22.0)	[redacted]
Placebo (N=186)	13/177 (7.3)	[redacted]

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group.

Table 21: HRQoL endpoint: MCS response in all patients using observed data, Week 16, FAS

Treatment group	n/M (%)	95% CI
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; FAS, full analysis set; HRQoL, health-related quality of life; M, number of patients in the treatment group of the specified analysis set; MCS, Mental component summary score; n, number of patients responded; N, number of patients in the randomised treatment group.

Table 22: HRQoL endpoint: PCS response in all patients using observed data, Week 16, FAS

Treatment group	n/M (%)	95% CI
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; FAS, full analysis set; HRQoL, health-related quality of life; M, number of patients in the treatment group of the specified analysis set; n, number of patients responded; N, number of patients in the randomised treatment group; PCS, Physical component summary score.

Table 23: HRQoL endpoint: FACIT-Fatigue change from baseline in all patients using observed data, Week 16, FAS

Treatment group	n	Mean change (SD)
Secukinumab 150 mg Load (N=185)	184	[redacted]
Secukinumab 150 mg No Load (N=184)	180	[redacted]
Placebo (N=186)	180	[redacted]

Abbreviations: FACIT, Functional Assessment of Chronic Illness Therapy; FAS, full analysis set; HRQoL, health-related quality of life; n, number of subjects with measures at both baseline and the corresponding post baseline visit; N, number of patients in the randomised treatment group; SD, standard deviation.

Table 24: HRQoL endpoint: EQ5D health state assessment change from baseline in all patients using observed data, Week 16, FAS

Treatment group	n	Mean change (SD)
Secukinumab 150 mg Load (N=185)	181	[redacted]
Secukinumab 150 mg No Load (N=184)	176	[redacted]
Placebo (N=186)	178	[redacted]

Abbreviations: EQ5D, Euro-QoL 5-Dimension Health Status Questionnaire; FAS, full analysis set; HRQoL, health-related quality of life; n, number of subjects with measures at both baseline and the corresponding post baseline visit; N, number of patients in the randomised treatment group; SD, standard deviation.

Table 25: HRQoL endpoint: Summary of WPAI-GH change from baseline in all patients using observed data, Week 16, FAS (as presented in Table 33 in CS, page 66)

Original treatment	Current treatment	n	Mean	SD
Percent work time missed due to health				
Secukinumab 150 mg Load (N=185)	Secukinumab 150 mg Load	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	Secukinumab 150 mg No Load	[redacted]	[redacted]	[redacted]
Placebo (N=186)	Placebo	[redacted]	[redacted]	[redacted]
Percent impairment while working due to health				
Secukinumab 150 mg Load (N=185)	Secukinumab 150 mg Load	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	Secukinumab 150 mg No Load	[redacted]	[redacted]	[redacted]
Placebo (N=186)	Placebo	[redacted]	[redacted]	[redacted]
Percent overall work impairment due to health				
Secukinumab 150 mg Load (N=185)	Secukinumab 150 mg Load	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	Secukinumab 150 mg No Load	[redacted]	[redacted]	[redacted]
Placebo (N=186)	Placebo	[redacted]	[redacted]	[redacted]
Percent activity impairment due to health				
Secukinumab 150 mg Load (N=185)	Secukinumab 150 mg Load	[redacted]	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	Secukinumab 150 mg No Load	[redacted]	[redacted]	[redacted]
Placebo (N=186)	Placebo	[redacted]	[redacted]	[redacted]

Abbreviations: FAS, full analysis set; HRQoL, health-related quality of life; n, number of subjects with measures at both baseline and the corresponding post baseline visit; N, number of subjects in each treatment group of the specified analysis set; SD, standard deviation; WPAI-GH, Work Productivity and Activity Impairment - General Health.

Table 26: Summary of exploratory analyses, Week 16, FAS

BASMI: Cervical rotation angle score change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]

BASMI: Lumbar flexion (modified Schober) score change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]
BASMI: Lateral lumbar flexion score change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]
BASMI: Maximal intermalleolar distance score change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]
BASMI: Tragus-to-wall distance score change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]
MASES change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	182	[redacted]
Secukinumab 150 mg No Load (N=184)	176	[redacted]
Placebo (N=186)	179	[redacted]
ASDAS-CRP change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	175	–1.289 (1.2551)
Secukinumab 150 mg No Load (N=184)	175	–1.279 (1.1817)
Placebo (N=186)	175	–0.738 (0.9638)
ASDAS-ESR change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]
ASDAS-CRP clinically important improvement in all patients using observed data		
Treatment group	**n/M (%)**	**95% CI**
Secukinumab 150 mg Load (N=185)	91/175 (52.0)	[redacted]
Secukinumab 150 mg No Load (N=184)	98/175 (56.0)	[redacted]
Placebo (N=186)	57/175 (32.6)	[redacted]
ASDAS-ESR clinically important improvement in all patients using observed data		

Treatment group	n/M (%)	95% CI
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]
ASDAS-CRP major improvement in all patients using observed data		
Treatment group	**n/M (%)**	**95% CI**
Secukinumab 150 mg Load (N=185)	46/175 (26.3)	[redacted]
Secukinumab 150 mg No Load (N=184)	47/175 (26.9)	[redacted]
Placebo (N=186)	18/175 (10.3)	[redacted]
ASDAS-ESR major improvement in all patients using observed data		
Treatment group	**n/M (%)**	**95% CI**
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]
ASDAS-CRP inactive disease in all patients using observed data		
Treatment group	**n/M (%)**	**95% CI**
Secukinumab 150 mg Load (N=185)	38/178 (21.3)	[redacted]
Secukinumab 150 mg No Load (N=184)	40/176 (22.7)	[redacted]
Placebo (N=186)	15/175 (8.6)	[redacted]
ASDAS-ESR inactive disease in all patients using observed data		
Treatment group	**n/M (%)**	**95% CI**
Secukinumab 150 mg Load (N=185)	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	[redacted]	[redacted]
Placebo (N=186)	[redacted]	[redacted]
Adjusted swollen 44 joint count change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	64	[redacted]
Secukinumab 150 mg No Load (N=184)	75	[redacted]
Placebo (N=186)	66	[redacted]
Adjusted tender 44 joint count change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	128	[redacted]
Secukinumab 150 mg No Load (N=184)	126	[redacted]
Placebo (N=186)	120	[redacted]
Inflammation represented by duration and severity of morning stiffness (mean of BASDAI questions 5 and 6) change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	181	[redacted]
Secukinumab 150 mg No Load (N=184)	177	[redacted]
Placebo (N=186)	177	[redacted]
Patient's global assessment of disease activity change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	176	[redacted]
Secukinumab 150 mg No Load (N=184)	176	[redacted]
Placebo (N=186)	177	[redacted]

Patient's assessment of back pain (total and nocturnal) change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	180	[redacted]
Secukinumab 150 mg No Load (N=184)	177	[redacted]
Placebo (N=186)	177	[redacted]
ASspiMRI-a change from baseline in all patients using observed data		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	179	[redacted]
Secukinumab 150 mg No Load (N=184)	177	[redacted]
Placebo (N=186)	176	[redacted]
ESR change from baseline in all patients (as presented in Table 34 in CS, page 70)		
Treatment group	**n**	**Mean change (SD)**
Secukinumab 150 mg Load (N=185)	179	[redacted]
Secukinumab 150 mg No Load (N=184)	177	[redacted]
Placebo (N=186)	176	[redacted]

Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; ASspiMRI-a, Ankylosing spondylitis spine MRI score for activity; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, confidence interval; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; FAS, full analysis set; M, number of patients in the treatment group of the specified analysis set; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; n, (for continuous outcomes) number of subjects with measures at both baseline and the corresponding post baseline visit, (for binary outcomes) number of patients responded; N, number of subjects in each treatment group of the specified analysis set; N/A, not applicable; SD, standard deviation.

A14. If the company cannot provide the data requested in question A13 please provide instead a "complete case" analysis for all outcomes at 16 weeks. That is, an analysis that excludes all drop-outs and patients with insufficient data to estimate outcomes.

Response: Not applicable. Data provided in response to question A13.

A15. PRIORITY. Could the company please provide results of analyses restricted to patients who have previously received a TNFα inhibitor? Please provide for all primary and secondary outcomes at 16 weeks.

Response: Section B.2.7.2 of the CS and Appendix E of the CS present results for primary and secondary endpoints split by TNF-naïve patients and patients who have previously received a TNFα inhibitor (i.e., patients who are labelled as TNF-IR in the CS). This data is Week 16 data.

We would like to note that there was a duplication of the header 'BASFI change from baseline using MMRM' in Appendix E. To clarify, in the table presenting subgroup data according to previous biological treatment experience, Rows 22 to 25 relate to

BASFI change from baseline and Rows 26 to 29 relate to MRI SI joint oedema score change from baseline as detailed in Table 27.

Table 27: Clarification of BASFI change from baseline and MRI SI joint oedema score change from baseline data, according to previous biological treatment experience, Week 16, FAS

Treatment group	Comparison	TNFα inhibitor-naïve	TNF-IR
BASFI change from baseline using MMRM			
		LS mean treatment contrast (95% CI)	
Secukinumab 150 mg Load	vs No Load	[redacted]	[redacted]
	vs placebo	[redacted]	[redacted]
Secukinumab 150 mg No Load	vs placebo	[redacted]	[redacted]
MRI SI joint oedema score change from baseline using ANCOVA based on multiple imputation			
		Estimate (SE)	
Secukinumab 150 mg Load	vs No Load	[redacted]	[redacted]
	vs placebo	[redacted]	[redacted]
Secukinumab 150 mg No Load	vs placebo	[redacted]	[redacted]

Abbreviations: ANCOVA, analysis of covariance; BASFI, Bath Ankylosing Spondylitis Functional Index; CI, confidence interval; FAS, full analysis set; LS, least squares; MMRM, mixed-effect model repeated measures; MRI, magnetic resonance imaging; SE, standard error; SI, sacroiliac; TNF-α, tumour necrosis factor – alpha; TNF-IR, tumour necrosis factor – inadequate response,

A16. PRIORITY. The ERG notes that there is some doubt as to whether secukinumab is effective in patients who are MRI or CRP negative [CS, B.2.7.1]. To permit further investigation could the company please provide the following data for all primary and secondary outcomes at 16 weeks:

For each treatment arm and each subgroup (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+):

- Number of patients
- [For binary outcomes] Number of observed events/responses
- [For continuous outcomes] Mean difference from baseline, with its SD

This could be either complete case data or with non-responder imputations.

Response: Table 28 presents the data requested for primary and secondary endpoints split by objective signs of inflammation (CRP+/MRI+, CRP+/MRI–, CRP–/MRI+). This is imputed, Week 16 data. Further data for each outcome (including odds ratios and LS mean treatment contrast) are presented in Section B.2.7.2 and Appendix E of the CS.

Table 28: Primary and secondary endpoint data, according to objective signs of inflammation, Week 16, FAS

Stratification group	Treatment group	n/M (%) or n	LS mean change (SE)
ASAS40 response in TNFα inhibitor-naive patients using non-responder imputation			
CRP+ and MRI+	Secukinumab 150 mg Load (N=49)	[redacted]	N/A
	Secukinumab 150 mg No Load (N=52)	[redacted]	
	Placebo (N=50)	[redacted]	
CRP+ and MRI–	Secukinumab 150 mg Load (N=45)	[redacted]	
	Secukinumab 150 mg No Load (N=44)	[redacted]	
	Placebo (N=45)	[redacted]	
CRP– and MRI+	Secukinumab 150 mg Load (N=70)	[redacted]	
	Secukinumab 150 mg No Load (N=70)	[redacted]	
	Placebo (N=76)	[redacted]	
ASAS40 response in all patients using non-responder imputation			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted] (53.7)	N/A
	Secukinumab 150 mg No Load (N=57)	[redacted] (50.9)	
	Placebo (N=55)	[redacted] (21.8)	
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted] (34.6)	
	Secukinumab 150 mg No Load (N=51)	[redacted] (31.4)	
	Placebo (N=51)	[redacted] (29.4)	
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted] (34.2)	
	Secukinumab 150 mg No Load (N=76)	[redacted] (39.5)	
	Placebo (N=80)	[redacted] (31.3)	
ASAS 5/6 response using non-responder imputation			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted]	N/A
	Secukinumab 150 mg No Load (N=57)	[redacted]	
	Placebo (N=55)	[redacted]	
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted]	
	Secukinumab 150 mg No Load (N=51)	[redacted]	
	Placebo (N=51)	[redacted]	
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted]	
	Secukinumab 150 mg No Load (N=76)	[redacted]	
	Placebo (N=80)	[redacted]	
BASDAI change from baseline using MMRM			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=57)	[redacted]	[redacted]
	Placebo (N=55)	[redacted]	[redacted]
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=51)	[redacted]	[redacted]
	Placebo (N=51)	[redacted]	[redacted]
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=76)	[redacted]	[redacted]
	Placebo (N=80)	[redacted]	[redacted]

BASDAI50 response using non-responder imputation			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted](46.3)	N/A
	Secukinumab 150 mg No Load (N=57)	[redacted](43.9)	
	Placebo (N=55)	[redacted](12.7)	
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted](32.7)	
	Secukinumab 150 mg No Load (N=51)	[redacted](33.3)	
	Placebo (N=51)	[redacted](25.5)	
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted](34.2)	
	Secukinumab 150 mg No Load (N=76)	[redacted](35.5)	
	Placebo (N=80)	[redacted](23.8)	
BASFI change from baseline using MMRM			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=57)	[redacted]	[redacted]
	Placebo (N=55)	[redacted]	[redacted]
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=51)	[redacted]	[redacted]
	Placebo (N=51)	[redacted]	[redacted]
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=76)	[redacted]	[redacted]
	Placebo (N=80)	[redacted]	[redacted]
ASAS20 response using non-responder imputation			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted]	N/A
	Secukinumab 150 mg No Load (N=57)	[redacted]	
	Placebo (N=55)	[redacted]	
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted]	
	Secukinumab 150 mg No Load (N=51)	[redacted]	
	Placebo (N=51)	[redacted]	
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted]	
	Secukinumab 150 mg No Load (N=76)	[redacted]	
	Placebo (N=80)	[redacted]	
SF-36 PCS change from baseline using MMRM			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=57)	[redacted]	[redacted]
	Placebo (N=55)	[redacted]	[redacted]
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=51)	[redacted]	[redacted]
	Placebo (N=51)	[redacted]	[redacted]
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=76)	[redacted]	[redacted]
	Placebo (N=80)	[redacted]	[redacted]

SF-36 MCS change from baseline using MMRM			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=57)	[redacted]	[redacted]
	Placebo (N=55)	[redacted]	[redacted]
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=51)	[redacted]	[redacted]
	Placebo (N=51)	[redacted]	[redacted]
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=76)	[redacted]	[redacted]
	Placebo (N=80)	[redacted]	[redacted]
ASQoL change from baseline using MMRM			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=57)	[redacted]	[redacted]
	Placebo (N=55)	[redacted]	[redacted]
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=51)	[redacted]	[redacted]
	Placebo (N=51)	[redacted]	[redacted]
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=76)	[redacted]	[redacted]
	Placebo (N=80)	[redacted]	[redacted]
ASAS partial remission using non-responder imputation			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted](29.6)	N/A
	Secukinumab 150 mg No Load (N=57)	[redacted](21.1)	
	Placebo (N=55)	[redacted](5.5)	
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted](21.2)	
	Secukinumab 150 mg No Load (N=51)	[redacted](19.6)	
	Placebo (N=51)	[redacted](7.8)	
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted](16.5)	
	Secukinumab 150 mg No Load (N=76)	[redacted](22.4)	
	Placebo (N=80)	[redacted](7.5)	

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CI, confidence interval; CRP, c-reactive protein; FAS, full analysis set; LS, least squares; MCS, mental component summary; MMRM, mixed-effect model repeated measures; MRI, magnetic resonance imaging; N/A, not applicable; OR, odds ratio; PCS, physical component summary; SE, standard error; SF-36, short form-36.

The PREVENT study demonstrated that all subgroups with objective signs of inflammation (CRP+/MRI+, CRP+/MRI–, CRP–/MRI+) derive benefit from treatment with secukinumab, while in terms of safety there is no increase in risk for each subgroup.

[redacted]

[redacted] It is acknowledged that these subgroups, although predefined in the exploratory analyses, are relatively small in size and thus not powered to derive definitive conclusions, but rather to demonstrate trends.

Furthermore, evidence in ankylosing spondylitis (AS) suggests that TNFα inhibitors may also be less effective in patients with lower CRP levels [5]. In a post-hoc analysis of etanercept trials in AS, very high baseline CRP was a significant predictor of 12-week outcomes [6].

A17. Given the apparent similarity in outcomes between “load” and “non-load” arms, could the company please provide results of analyses where the two active arms are combined, compared to placebo? Please provide for all primary and secondary outcomes at 16 weeks.

Response: We do not consider it appropriate to pool results from the Load and No-Load arms, for the reasons listed below. However, to accommodate this request we have provided an analysis using simple arithmetic pooling in the reference pack [7].

- Load and No Load are considered separate interventions; the Novartis regulatory submission to the EMA defines the secukinumab trial arms as two separate intervention groups, and it is expected that the EMA licence will be for the Load regimen. The primary objective under Analysis Plan A (for the EU and other non-USA regions) was to demonstrate the superiority of secukinumab 150 mg Load over placebo at Week 16 in TNF-naïve patients with active nr-axSpA based on the proportion of patients achieving an ASAS40 response. The No Load regimen was included to meet the requirements of the US Food and Drug Administration (Analysis Plan B).

- The Load arm includes three additional loading doses, and this had pharmacokinetic implications in PREVENT.
  [redacted]

[redacted]There was a consistent trend towards numerically higher (although not statistically significant) efficacy responses with the Load regimen within the first 16 weeks, likely due to the inclusion of three additional loading doses and the observed differences in pharmacokinetics.

Pooling of the two secukinumab interventions will therefore violate rules of evidence synthesis methodology and will be misaligned with the future EMA regulatory label.

Network meta-analysis

A18. PRIORITY. Could the company please provide results for all NMAs performed in the form of complete results matrices (as in CS appendix D.4.2). Specifically, please provide results for all outcomes for:

- Identical treatment effect for anti-TNFs models
- Placebo adjusted models
- Models using vague, Turner's and truncated Turner priors

Response: Results (including those in the form of results matrices) are provided in the reference pack [8]. Note that the placebo-adjusted analyses lack robustness and results should be interpreted with caution.

A19. PRIORITY. Please provide the data sets and models used for the NMA, sufficient for the ERG to reproduce the NMA analyses. In addition, for all NMAs please provide the predicted Bayesian treatment rankings (with credible intervals), and SUCRA curves.

Response: Data sets and models are provided in the reference pack [8]. Note that the Bayesian treatment rankings are not very informative, especially in the event of small networks (e.g. some of the analyses with only PBO, SEC and COMPARATOR), but are provided for completeness as supportive output. Limited weight should be attributed to such rankings. It was not considered necessary to supply the SUCRA curves as rankings have been provided.

A20. PRIORITY. In the NMAs, was analysis of secukinumab based on the "Load" or "Non-load" arms? Could the company please provide NMAs for all main outcomes

with the load and non-load arms combined (as in question A17)? Please include the predictive distribution of the anti-TNF class-effect with the results.
Response: Results of analyses using simple arithmetic to generate combined estimates are provided in the reference pack [7].

A21. PRIORITY. Given the concerns as to whether secukinumab is effective in patients who are MRI or CRP negative (question A16), can the company provide any indirect comparison evidence in the CRP+/MRI+, CRP+/MRI-, CRP-/MRI+ subgroups, where evidence is available in trials of TNFα inhibitors? This could consist of NMAs where there are sufficient data; indirect comparisons between PREVENT and other single trials; a narrative commentary or summary. If possible, please also consider indirect comparisons for MRI+ and MRI- groups (that is, without considering CRP).
Response: A review of existing literature found that relevant subgroup data was only available from the EMBARK trial, evaluating etanercept against placebo, for which ASAS40 and BASDAI 50 results according to CRP+/- and MRI+/- status were reported [9].
An indirect treatment comparison (ITC) was therefore conducted based on reported subgroup results from PREVENT and EMBARK. To evaluate relative efficacy between secukinumab and etanercept, an ITC using Bucher's method [10] was conducted, with placebo as the common comparator arm. Relative efficacy estimates are presented in the form of odds ratios (OR) along with associated 95% confidence intervals (CI). Results are shown in Table 29 for secukinumab vs etanercept.

Table 29: Results from the Bucher ITC analyses for MRI and CRP subgroups

Outcome	Group	OR (95% CI)
ASAS40	CRP -/MRI +	[redacted]
ASAS40 †	CRP +/MRI -	[redacted]
ASAS40	CRP +/MRI +	[redacted]
BASDAI50	CRP -/MRI +	[redacted]
BASDAI50 †	CRP +/MRI -	[redacted]
BASDAI50	CRP +/MRI +	[redacted]
ASAS40	Any CRP/MRI +	[redacted]
BASDAI50	Any CRP/MRI +	[redacted]
ASAS40 †	CRP +/Any MRI	[redacted]
BASDAI50 †	CRP +/Any MRI	[redacted]

†Correction factor of 0.5 applied as zero response is present in CRP+/MRI- subgroup in EMBARK study.
Abbreviations: CI, confidence interval; CRP, C-reactive protein; MRI, magnetic resonance imaging; OR, odds ratio.

The ITC results indicate that secukinumab is better that etanercept (RR>1) for 6 out of 10 subgroups considered. However, none of the odds ratio are statistically significant, noted by inclusion of 1 in the 95% confidence interval. Please refer to the limitations section below for additional insights.

EMBARK and PREVENT were deemed comparable with similar baseline characteristics and patient populations. However, a few differences between these trials are noted:

- EMBARK enrolled CRP- and MRI- patients, in addition to patients with Objective Signs of Inflammation (OSI), whereas PREVENT only enrolled patients with OSI. For the present analysis we considered only the OSI subgroup patients in EMBARK (patients with CRP+ and/or MRI+)
- Although trial baseline characteristics were broadly similar, a few differences were noted in mean age, baseline BASDAI and baseline BASFI

Limitations of the above analyses are given below:

- Relevant data for EMBARK were extracted digitally from graphs presented in the publication. As a result, there may be a loss of accuracy.
- Bucher ITC methodology is a simplistic approach to compare two treatments in the absence of head to head data.
- There is a high degree of uncertainty with respect to the results, mostly attributed to low sample sizes of the subgroups

Background data sets and calculations of the Bucher ITC analyses are provided in the reference pack [11].

A22. Could the company please provide more detail on the exact statistical models used to conduct the joint NMA of BASFI and BASDI.
Response: The section below provides an overview of the joint models implemented within an NMA. The relevant BUGS model files are also provided in the reference pack [12].
BASDAI 50 and BASDAI CFB (which are both based on BASDAI scores) are synthesised in one analysis. BASDAI 50 is measured as the probability of having a reduction in BASDAI score of 50%. Hence, the proportion of BASDAI 50 responders can be connected to the change from baseline in absolute BASDAI scores observed in each study. This model can also be extended to incorporate change from baseline in BASFI scores. This approach is the same as the one preferred in the base case analysis in a previous NICE Technology Appraisal (TA383) [13] for AS and nr-axspa. Therefore, an NMA informed by Model B and Model C in TA383 [13] was conducted to jointly model BASDAI 50, BASDAI CFB and BASFI CFB scores.

A brief description of these models and an overview of terminology used in this analysis is presented in Table 30:

Table 30: Description and terminology of joint models for BASDAI and BASFI

Description	Terminology used in TA 383	Terminology used in the present analysis
Joint modelling of BASDAI50 and BASDAI CFB	Model B	joint_BASDAI50_BASDAIcfb
Joint modelling of BASDAI50 and BASDAI CFB, along with correlation with BASFI CFB	Model C	joint_correlated_BASDAI50_BASDAIcfb _BASFIcfb

The joint models detailed in TA383 were modified in order to suit the requirements of the analysis. Three versions of the basic model were implemented. These are specified as follows:

1) Joint modelling and correlation included, however no exchangeability was assumed

In this case the treatment effect parameters, d, were assigned to prior distributions directly. Mathematically, this refers to Equation 49 (Model B) in TA383. In this case, the BASDAI treatment effect parameter, d, is modified to be:

$$d_k \sim N(0,1000)\ for\ k \neq 1;\ d_k = 0\ otherwise$$

A similar change was made for Model C for both BASDAI and BASFI parameters. Model files ModelBAlldiff.txt and ModelCAlldiff.txt detail the NMA code.

2) Joint modelling and correlation included, however exchangeability amongst ALL treatments was assumed

In this case, the treatment effect parameters were assumed to follow a common distribution with mean effect and sd, and prior distributions were assigned to these parameters. Mathematically, this refers to Equation 49 (Model B) as well as Equation 55 (Model C) in TA383. The same model is used in this case. Model files ModelBAllExch.txt and ModelCAllExch.txt detail the NMA code.

3) Joint modelling and correlation included, however no exchangeability amongst ALL anti-TNFs was assumed

In this case, the treatment effect parameters (except secukinumab) were assumed to follow a common distribution with mean effect and sd, and prior distributions were assigned to these parameters. For secukinumab, the treatment effect parameter was assigned to a prior distribution directly. Mathematically, this refers to Equation 49 (Model B) in TA383. In this case, the BASDAI treatment effect parameter d is modified to be:

$$d_k \sim N(D, sd.re)\ for\ k \neq 1,6;\ d_1 = 0$$
$$D \sim N(0,0.001), sd.re \sim U(0,2)$$
$$d_k \sim N(0,1000)\ for\ k = 6\ which\ represents\ treatment\ effect\ of\ secukinumab$$

A similar change was made for Equation 55 (Model C) for both BASDAI and BASFI parameters. Model files ModelBAntiTNFExch.txt and ModelCAntiTNFExch.txt detail the NMA code.

Relevant codes are provided in the reference pack [12].

Section B: Clarification on cost-effectiveness data

Cost effectiveness in general

B1. PRIORITY. As per questions A17 and A20, could the company please re-run all cost effectiveness analyses using NMA results where the load and non-load arms in the PREVENT trial are combined?

Response: We do not consider it appropriate to pool results from the Load and No Load arms; however, a scenario analysis will be provided on Tuesday 4th February based on the analysis described in Question A17 (i.e. simple arithmetic pooling).

B2. PRIORITY. The supplied economic model uses the shrunken estimates from the class effect NMA model to inform the effectiveness of the different TNFα inhibitors. Could the company please re-evaluate cost-effectiveness using the predictive distribution of the class-effect to represent a single effect estimate for TNFα inhibitors (as was done in the MTA [TA383])? This will entail simplifying the economic model to consider only one TNFα inhibitor comparator (to represent the class) whose cost is based on the 'mixed-basket' approach (excluding secukinumab). Please use the pooled evidence from load and no-load arms of the PREVENT trial (as requested in B1).

Response: The following changes have been made to the cost-effectiveness model for this scenario:

- Efficacy is based on the TNFα inhibitor exchangeable joint correlated BASDAI50, BASDAI change from baseline and BASFI change from baseline NMA model (i.e. efficacy is estimated for all TNFα inhibitors as a class; see Table 31)

- Drug costs and adverse event frequencies for TNFα inhibitors are calculated as a weighted average based on available market share data

Previous pooling analyses to investigate a class effect of TNFα inhibitors have been conducted in TA383, however, it was noted that "The Assessment Group reported that statistical heterogeneity was apparent in the analyses, and therefore the reliability of the pooled estimates, and their true relevance to people seen in clinical

practice, is questionable. Estimates of the class effect of TNF alpha inhibitors were consistently smaller in non radiographic axial spondyloarthritis compared with those seen in ankylosing spondylitis trials (most noticeably for BASFI and BASDAI 50)". It is also noted that even if efficacy is assumed to be equivalent across TNFα inhibitors, drug costs differ substantially; the cost-effectiveness of secukinumab compared with each TNFα inhibitor is therefore expected to differ.

At this stage, no amends have been made to the model to use pooled results (based on simple arithmetic pooling) from the Load and No Load arms (see Questions A17 and B1); an updated scenario including this change will be provided on Tuesday 4th February.

The results of this scenario are presented in Table 32. Secukinumab is shown to be a highly cost-effective treatment option.

Table 31: Efficacy data used in scenario analysis

Treatment	BASDAI 50	Baseline BASDAI		Baseline BASFI		BASDAI change from baseline		BASFI change from baseline	
		R	NR	R	NR	R	NR	R	NR
CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TNFα inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care; NR, non-responder; R, responder; TNFα, Tumour necrosis factor alpha.

Table 32: Results of scenario analysis

Treatment	Total costs	Total QALYs	Incremental costs vs. CC	Incremental QALYs vs. CC	ICER vs. CC	ICER (fully incremental)
CC	[redacted]	[redacted]	-	-	-	-
Secukinumab	[redacted]	[redacted]	£7,684	1.03	£7,460	£7,460
TNFα inhibitor	[redacted]	[redacted]	£21,648	1.62	£13,363	£23,667

Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TNFα, Tumour necrosis factor alpha.

B3. PRIORITY. Please explain in detail the modelling of sequences and all the assumptions involved. In particular, please detail how the model considers BASFI scores at the start of second line treatment, and progression in BASFI thereafter. In the ERG's first reading of the model it seems that a patient starting second line treatment is attributed the baseline BASFI score. If so, please correct the model to reflect the patient's BASFI score after the duration of first line treatment.

Response: The ERG is correct that the submitted model assumed that BASFI score at the start of second-line treatment is equivalent to the first-line baseline BASFI score. The model has now been corrected in line with Table 33.

In the scenario in which treatment sequencing is considered, all patients discontinuing from their initial biologic therapy are assumed to move on to a second-line biologic. The second-line biologic is assumed to be a weighted average of all treatments other than the initial biologic therapy (hereafter referred to as the component therapies); this weighting is based on available market share data (see Question B9b).

This scenario is only available for the primary analysis (i.e. the analysis in which patients who enter the model are biologic-naïve).

Model inputs used in the sequencing scenario are presented in Table 33; assumptions around changes in BASDAI and BASFI following non-response and discontinuation, and changes in BASFI over time, are the same as for first-line therapy (see Question B14).

Table 33: Model inputs used in sequencing scenario

Model input	Approach

Second-line response	• As for first-line therapy, response to second-line therapy is assessed 12-16 weeks after initiation (modelled as 3 months)
	• An option is included to apply a reduction in efficacy for second-line therapy compared with first-line therapy
	  ○ If this option is selected, the ratio between response rates for biologic-naïve and biologic-experienced patients in PREVENT is assumed to apply to all biologics
	  ○ If this option is not selected, second-line efficacy is assumed to be equivalent to first-line efficacy
	• The response rate for the weighted second-line therapy is calculated as the weighted average of the estimated second-line response rates for the component therapies

Second-line baseline BASDAI	• Second-line baseline BASDAI is calculated as the weighted average of first-line baseline BASDAI for the component therapies
Second-line baseline BASFI	• Second-line baseline BASFI is calculated as the weighted average of the BASFI observed at the median cycle of discontinuation from first-line therapy (i.e. the time point at which 50% of responders had discontinued) for the component therapies
Second-line BASDAI and BASFI changes from baseline	• An option is included to apply a reduction in efficacy for second-line therapy compared with first-line therapy ○ If this option is selected, the ratio between changes from baseline for biologic-naïve and biologic-experienced patients in PREVENT is assumed to apply to all biologics

	○ If this option is not selected, second-line efficacy is assumed to be equivalent to first-line efficacy • The changes from baseline for the weighted second-line therapy is calculated as the weighted average of the estimated second-line changes from baseline for the component therapies

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

B4. PRIORITY. Could the company please re-evaluate cost-effectiveness by comparing the following treatment sequencing scenarios:

a. Secukinumab in first line, followed by a TNFα inhibitor in 2nd-line,

b. TNFα inhibitor in first line followed by secukinumab in 2nd-line,

c. TNFα inhibitor in first line followed by another TNFα inhibitor in 2nd-line.

Please use the pooled evidence from load and no-load arms of the PREVENT trial (as in B1) and a single effect estimate for TNFα inhibitors (as in B2). Assume that 100% of patients move to 2nd-line. Please identify and use evidence from trials and/or registries relating to the reduction in efficacy of TNFα inhibitors in 2nd-line. Please reproduce and report all scenario and sensitivity analyses. Consider alternative scenarios where the treatment effect of secukinumab is i) maintained and ii) reduced at 2nd-line.

Response: The requested analysis is considered to be subject to substantial uncertainty because:

- No data are available on the efficacy of TNFα inhibitors in biologic-experienced patients
- Efficacy data in biologic-experienced patients from PREVENT is based on low patient numbers (21 and 15 patients in the secukinumab load and placebo arms, respectively)
- As in Question B2, the cost-effectiveness of secukinumab is expected to differ when compared with each TNFα inhibitor; an ‘average’ TNFα inhibitor does not exist in practice and cannot be prescribed to a patient

- Following the use of the most cost-effective TNFα inhibitor, this therapy would no longer be available as an option in later lines, but is informing the average cost for subsequent treatment, therefore the analysis is limited in its relevance for treatment decision making

- The only TNFα inhibitor that secukinumab is not cost-effective against is biosimilar adalimumab; positioning secukinumab any later than second line (as in the scenario in which a TNFα inhibitor is used both first and second line) is not considered appropriate

- The requested analysis does not reflect clinical expert advice (see Question B7). Switching to a biologic with a new mechanism of action is expected to be more effective than switching within class

However, an assumption-based analysis has been provided.

In this analysis, a single effect estimate has been applied for TNFα inhibitors (as in Question B2) and 100% of patients have been assumed to receive a second-line biologic following discontinuation from first-line therapy.

The second-line efficacy for all biologic therapies is assumed to be reduced by the same proportion as observed in the secukinumab arm of PREVENT (i.e. the ratio between outcomes for biologic-experienced and biologic-naïve patients); no relevant data were identified to inform second-line efficacy for TNFα inhibitors. This assumption is considered to be reasonable on the basis of evidence from Navarro-Compan et al which shows that the reduction in efficacy at second line is not dependent on the type of biological disease-modifying anti-rheumatic drug [14].

As requested by the ERG, two analyses are considered in which:

- The secukinumab treatment effect is maintained at second line; a reduction is applied for TNFα inhibitors; or

- The treatment effect for both secukinumab and TNFα inhibitors is reduced at second line

At this stage, no amends have been made to the model to use pooled results (based on simple arithmetic pooling) from the Load and No Load arms (see Questions A17, B1 and B2); an updated scenario including this change will be provided on Tuesday 4th February.

The results of the two analyses are presented in Table 34 and Table 35.

The results of scenario analyses are presented in Table 36; for these scenarios, the treatment effect at second line is assumed to be reduced for both secukinumab and TNFα inhibitors. As discussed previously, the results of univariate and probabilistic sensitivity analysis will be provided on Tuesday 4th February.

Table 34: Base-case results (secukinumab treatment effect reduced at second line)

Treatment pathway	Total costs	Total QALYs	Incremental costs vs. baseline†	Incremental QALYs vs. baseline†	ICER vs. baseline†	ICER (fully incremental)
Secukinumab -> TNFα inhibitor	[redacted]	[redacted]	-	-	-	-
TNFα inhibitor -> TNFα inhibitor	[redacted]	[redacted]	£8,962	0.60	£14,936	£14,936
TNFα inhibitor -> secukinumab	[redacted]	[redacted]	£12,904	0.22	£58,654	Dominated

Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TNFα, Tumour necrosis factor alpha.
† The baseline is secukinumab -> TNFα inhibitor.

Table 35: Base-case results (secukinumab treatment effect maintained at second line)

Treatment pathway	Total costs	Total QALYs	Incremental costs vs. baseline†	Incremental QALYs vs. baseline†	ICER vs. baseline†	ICER (fully incremental)
Secukinumab -> TNFα inhibitor	[redacted]	[redacted]	-	-	-	-
TNFα inhibitor -> TNFα inhibitor	[redacted]	[redacted]	£8,962	0.60	£14,936	£14,936
TNFα inhibitor -> secukinumab	[redacted]	[redacted]	£12,077	0.75	£16,103	£20,769

Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TNFα, Tumour necrosis factor alpha.
† The baseline is secukinumab -> TNFα inhibitor.

Table 36: Results of scenario analysis

Area of uncertainty	Base case	Scenario	ICER for secukinumab -> TNFα inhibitor	
			vs. TNFα inhibitor -> secukinumab	vs. TNFα inhibitor -> TNFα inhibitor
Time horizon	Lifetime (maximum age of 100 years)	5 years	£ 17,398*	£10,553*
		10 years	£24,374*	£13,705*
		20 years	£35,161*	£14,887*
		40 years	£54,854*	£14,911*
Discounting	3.5% for costs and outcomes	No discounting	£126,948*	£15,164*
		3.5% for costs, 1.5% for outcomes	£60,126*	£11,932*

Area of uncertainty	Base case	Scenario	ICER for secukinumab -> TNFα inhibitor	
			vs. TNFα inhibitor -> secukinumab	vs. TNFα inhibitor -> TNFα inhibitor
Impact on BASDAI and BASFI following discontinuation	Reverse initial gain	Revert to natural history	£61,520*	£15,197*
Biologic-specific treatment effect on BASFI	Treatment effect implemented from beginning of maintenance treatment	Treatment effect implemented after 4 years	£60,095*	£14,955*
		No treatment effect	£60,994*	£15,278*
Utility model	Based on PREVENT	Model used by the assessment group for TA383	£40,935*	£12,724*
		Based on pooled PREVENT and MEASURE 1/2 data	£82,023*	£14,183*
		Model presented in McLeod et al	£46,156*	£11,703*
AE disutilities	Excluded	Included	£ 59,624*	£ 14,845*

*South-west quadrant.
Abbreviations: AE, adverse event; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

Scenario analyses and subgroups

B5. PRIORITY. Please provide a scenario analysis (using the model and comparisons in B4) that assumes common baselines for responders and non-responders. Please justify the baseline values used.

Response: In this scenario, the baseline BASFI for each comparator, and for both responders and non-responders, is modelled to be 6.09. The baseline BASDAI for each comparator, and for both responders and non-responders, is modelled to be 6.92. These values are the average baseline values observed in PREVENT across both trial arms.

At this stage, no amends have been made to the model to use pooled results (based on simple arithmetic pooling) from the Load and No Load arms (see Questions A17, B1, B2 and B4); an updated scenario including this change will be provided on Tuesday 4th February.

The results of this scenario and the submitted base-case model are presented in Table 37.

Table 37: Results of scenario analysis

	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER vs. baseline	ICER (fully incremental)
Submitted base-case model						
Conventional care	[redacted]	[redacted]	-	-	-	-
Adalimumab biosimilar	[redacted]	[redacted]	£3,086	1.63	£1,893	£1,893
Secukinumab	[redacted]	[redacted]	£6,692	1.07	£6,254	Dominated
Etanercept biosimilar	[redacted]	[redacted]	£24,526	1.52	£16,136	Dominated
Etanercept	[redacted]	[redacted]	£27,843	1.52	£18,318	Dominated
Certolizumab pegol	[redacted]	[redacted]	£27,927	1.74	£16,050	£225,827
Adalimumab	[redacted]	[redacted]	£28,316	1.63	£17,372	Dominated
Golimumab	[redacted]	[redacted]	£30,352	1.75	£17,344	£242,500
Sequencing model (reduced efficacy at second-line for secukinumab and TNFα inhibitors)						
Secukinumab -> TNFα inhibitor	[redacted]	[redacted]	-	-	-	-
TNFα inhibitor -> secukinumab	[redacted]	[redacted]	£3,162	0.42	£7,529	£7,529
TNFα inhibitor -> TNFα inhibitor	[redacted]	[redacted]	£8,568	0.62	£13,819	£27,027
Sequencing model (reduced efficacy at second-line for TNFα inhibitors only)						
Secukinumab -> TNFα inhibitor	[redacted]	[redacted]	-	-	-	-
TNFα inhibitor -> secukinumab	[redacted]	[redacted]	£1,063	0.03	£35,433	£35,433
TNFα inhibitor -> TNFα inhibitor	[redacted]	[redacted]	£7,758	-0.32	Dominated	Dominated

Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TNFα, Tumour necrosis factor alpha.

B6. PRIORITY. Given the concerns as to whether secukinumab is effective in patients who are MRI or CRP negative (Question A16 and A21), could the company please re-run the cost effectiveness analysis for the subgroups defined by MRI and CRP status (MRI+/CPR+ vs. MRI+/CRP- vs. MRI-/CRP+) and in the subgroups defined by MRI (MRI+ vs MRI-).

Response: The required data are not available for these subgroups for TNFα inhibitors[b]; it is therefore only possible to present a comparison between secukinumab and conventional care based on subgroup data from PREVENT.

[b] BASDAI50 data are available for etanercept patients from Brown et al [9]; however, this would not be sufficient to populate the cost-effectiveness model.

As discussed previously, a simple approach to this analysis will be provided on Tuesday 4th February. Results based on a formal subgroup analysis will be provided at a later date (to be agreed).

B7. PRIORITY. Could the company please model the cost-effectiveness of the use of secukinumab at last line of treatment; that is, in patients not eligible for a TNFα inhibitor? This analysis should consider the population characteristics (we suggest looking at patients in 3rd or 4th line of therapy with TNFα-inhibitors), should compare against conventional care, and should quantify the impact of a possible reduction in effectiveness of secukinumab relative to first line use.

Response: We do not believe that it would be appropriate in clinical practice to try multiple TNFα inhibitors following inadequate response if another treatment with a different mechanism of action is available, particularly for primary non-responders. The Regional Medicines Optimisation Committee (RMOC, South) statement on the sequential use of biological medicines [15] states:

"When a treatment fails, guidance from specialist bodies suggests switching to a biologic with a new mechanism of action is more effective than switching within class, although it should be noted that this is based on low quality evidence. The exception to this is secondary failure of anti-TNF treatment due to formation of anti-drug antibodies, in which case switching within class may be a valid treatment option."

Recent academic research suggests that IL-17A (the target of secukinumab) is a key cytokine driving axSpA pathology. Enthesitis is the primary inflammatory lesion in SpA and translational research suggests that this leads to bone destruction and reformation. At present there is a lack of translational data demonstrating the role of TNFα in driving this pathology.

IL-17A has been identified within unique populations of resident immune cells (e.g. ILC3 and gamma delta T cells) within spinal entheseal soft tissue, and has been implicated in driving mechanisms that are known to alter bone remodelling within the spine. Furthermore, animal models suggest that the molecular pathways driving the production of IL-17A and TNFα are independent of eachother. This is an ongoing area of research which warrants further investigation, however translating these

findings into human pathology could suggest that some patients may be responsive to specific mechanisms of action of different biologic agents (e.g. anti-TNF or anti-IL-17A therapy) [16-18].

This evidence further supports the need for a treatment with an alternative mode of action in nr-axSpA, and the importance of this for patients was discussed by the committee in TA407 [2]:

"The clinical experts stated that the novel mechanism of action of secukinumab, and its other marketing authorisations for psoriasis and psoriatic arthritis, would give patients and clinicians a greater choice of targeted treatment options.

A patient expert stated that it is particularly important to have the option of a treatment with a different mechanism of action for patients whose disease did not respond to one or more TNF-alpha inhibitors.

The committee concluded that the availability of an effective new treatment option would be valuable for people with active AS."

The CS provides results of analyses in TNF-IR populations (Section B.3.8), but we do not believe that performing an analysis in 3rd or 4th line would add value beyond this.

In addition to the uncertainty associated with the clinical relevance of the scenario, there is a lack of data on patient population characteristics, treatment efficacy in 3rd/4th line[c], and how treatment efficacy is affected by the reason for switching (as noted by the committee in TA383).

Issues with the supplied model

B8. PRIORITY. Please consider whether there is any recent information that could be used to update the long-term progression model that was originally used in the MTA [TA383] and adopted in the supplied economic model. For example, if possible, please provide a summary of the literature on recent/latest advances in nr-axSpA, considering specifically any evidence on the characteristics of this population (age,

c In PREVENT, 90.3% of patients had received no prior TNFα inhibitor, and 9.7% of patients had received one prior TNFα inhibitor.

gender, baseline BASDAI, baseline BASFI) and on their long-term progression in the disease.

Response: Three publications were identified that have become available subsequent to TA383 and document the progression rate from nr-axSpA to AS (Table 38). However, these data are not in the correct format to (either directly or indirectly) inform BASFI changes over time.

Table 38: Progression rates from nr-axSpA to AS

Factors leading to AS progression	Follow-up duration	% Progressed to AS	Source
Smoking, HLA-B27 positivity, active sacroiliitis on MRI	2 years	2.0%	Dougados et al, 2016 [19]
Elevated CRP, HLA-B27 positivity, active sacroiliitis on MRI	5 years	5.1%	Dougados et al, 2017 [20]
Low-grade sacroiliitis, axial disease	8.3 years	8.1%	Constantino et al, 2017 [21]

Abbreviations: AS, ankylosing spondylitis; CRP, C-reactive protein; MRI, magnetic resonance imaging.

B9. PRIORITY. Please clarify the following aspects relating to inputs or results included in the CS:

a. Please provide evidence of which inputs determine the increase in total costs for conventional care in relation to secukinumab for biologic experienced patients. [Table 83, page 157 of the CS]

   Response: Disaggregated costs for secukinumab and conventional care in the secondary analysis (biologic-experienced patients) are presented in Table 39. The conventional care arm is associated with higher total costs compared with the secukinumab arm; this is driven by a substantial difference in disease management costs (as determined by the following formula: £1,370.15 × exp[0.213 ×BASFI]).

   The key inputs determining the incremental costs for secukinumab vs conventional care are presented in Figure 5. Baseline BASFI for non-responders is found to be highly influential; however, given that these parameters cannot be considered to be independent from baseline values for responders (see Question B9c), but are varied as if this is the case, this result should be interpreted with caution. Other influential parameters are the BASFI

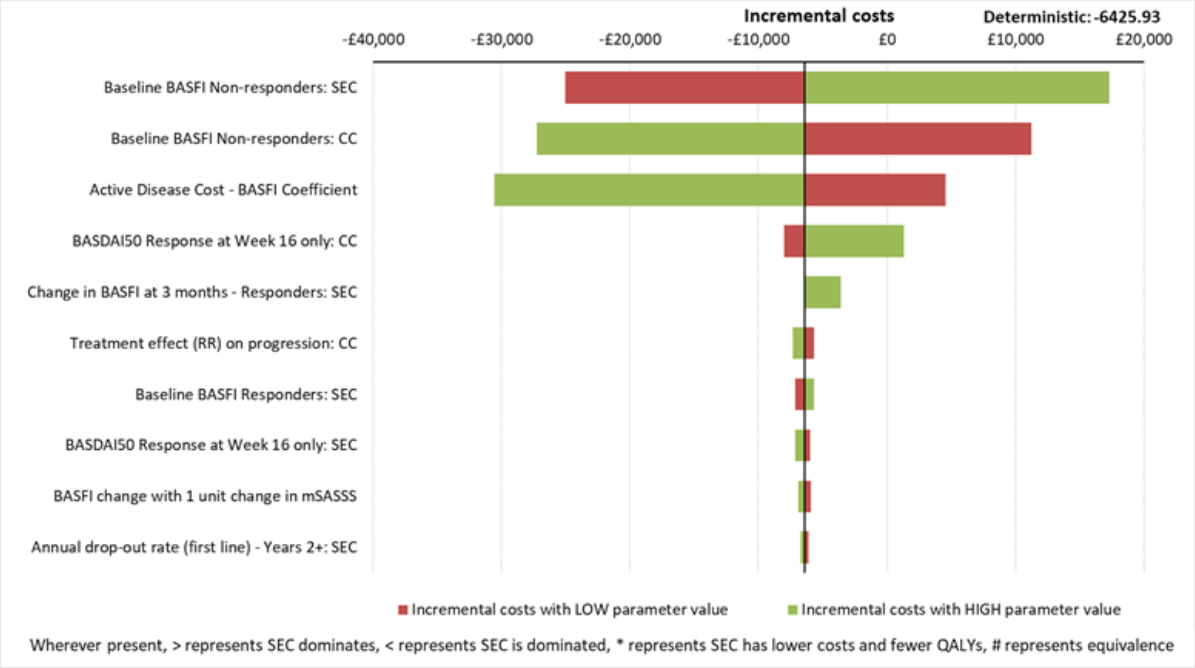
coefficient for the formula determining disease management costs and the BASDAI50 response rate for conventional care.

Table 39: Disaggregated costs – secondary analysis (biologic-experienced patients)

Type of cost	CC	Secukinumab	Incremental
Drug acquisition	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]
Total	£122,779	[redacted]	[redacted]

Abbreviations: CC, conventional care.

Figure 5: Univariate sensitivity analysis for cost savings (SEC vs. CC)



Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care; RR, relative risk; SEC, secukinumab.

b. Please provide further details on how the market share information, on which the 'mixed-basket' of second-line biologics is based on, was derived. The market share values in the decision model do not match the figures displayed in provided "Novartis data on file 2019 - market share data" reference, so please clarify what the values used in the model represent.

Response: The ERG is correct; the wrong reference for these data were provided in the company submission. The slide deck shared previously presents monthly patient shares; the updated Excel spreadsheet reference presents the average market share across all months in 2019 [22].

Market share data used in the cost-effectiveness model were generated from the referenced Excel spreadsheet as follows:

1. Market share data from the referenced Excel spreadsheet were rounded to one decimal place, and incorporated in the budget impact model as inputs
2. Market share data for infliximab and other were set to zero
3. The market share values were rescaled such that the total market share sums to 100%
4. These values were then copied into the cost-effectiveness model to ensure consistency between the two models

c. Please clarify how the baseline BASDAI and BASFI are calculated. Table 80, page 147 of the CS refers to Section B.3.3.2 of the CS, which does not provide any details.

Response: Differing baseline values for BASDAI and BASFI are assumed for responders and non-responders; this approach was also taken in TA383. However, there are two challenges in generating these data:

- Baseline values for responders and non-responders separately are only available for secukinumab, adalimumab and conventional care
- In order to present a fair comparison, the average baseline scores across responders and non-responders must be the same across all comparators (i.e. the same population must enter the model for each comparator)

An example is given for how baseline BASDAI scores were generated; the process for generating baseline BASFI scores is identical.

By rearranging the following formula, it is possible to calculate the responder and non-responder baselines if we know the overall baseline BASDAI, the response rate for each comparator, and the ratio between responder and non-responder baselines

- Overall BASDAI = Responder BASDAI x % response + Non-responder BASDAI x (1-% response)

The response rate for each comparator is known, and the overall baseline values were assumed to be the average baseline scores across all biologic-naïve patients in PREVENT.

Ratio between responder and non-responder baselines

Responder and non-responder baselines were only available from PREVENT and ABILITY-1 for secukinumab, adalimumab and conventional care (Table 40). The ratios between responder and non-responder baselines for other biologics were assumed to be the average of the ratios for secukinumab and adalimumab.

Table 40: Baseline BASDAI

	SEC‡	CER P	ETN	ADA†	GOL	CC‡	Average
Responder BASDAI	[redacted]	-	-	[redacted]	-	[redacted]	-
Non-responder BASDAI	[redacted]	-	-	[redacted]	-	[redacted]	-
Ratio of responder to non-responder BASDAI	[redacted]	-	-	[redacted]	-	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CC, conventional care; CER P, certolizumab pegol; GOL, golimumab; ETN, etanercept; SEC, secukinumab.
*Average excludes CC.
‡Responder and non-responder baselines collected from PREVENT.
†Responder and non-responder baselines collected from ABILITY-1, week 12.

Table 41: Re-calculated responder and non-responder baseline BASDAI scores

Technology	% responders	Responder BASDAI	Non-responder BASDAI	Applied ratio
SEC	[redacted]	[redacted]	[redacted]	[redacted]
CER P†	[redacted]	[redacted]	[redacted]	[redacted]
ETN†	[redacted]	[redacted]	[redacted]	[redacted]
ADA	[redacted]	[redacted]	[redacted]	[redacted]
GOL†	[redacted]	[redacted]	[redacted]	[redacted]
CC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CC, conventional care; CER P, certolizumab pegol; GOL, golimumab; ETN, etanercept; SEC, secukinumab.

d. The drug acquisition costs in the CS are the same as those used in the MTA. Please verify that these prices have not changed since 2014.

Response: We can confirm that the drug acquisition costs are based on current British National Formulary prices. These costs are the same as those presented in TA383, with the exception of the biosimilar prices for adalimumab and etanercept, which were not previously available.

B10. PRIORITY. Please clarify the following aspects relating to the supplied model Excel file as the ERG was unsuccessful in replicating the results in Table 83:

a. Please clarify why efficacy data in the "Sub Group Data" tab of the decision model are the same across all subgroups.

Response: The efficacy data presented in column E of the "Sub Group Data" sheet of the model are identical across the biologic-naïve, biologic-experienced and mixed populations[d] for two reasons:

1. The option to model a reduction in efficacy for the biologic-experienced and mixed populations as compared with the biologic-naïve population is currently set to "No" (see cell D58 on the "Settings" sheet)

2. When this parameter is set to "Yes", the efficacy data presented on the "Settings" sheet remains equivalent; however, this reduction in efficacy is then applied within the model calculation sheets (i.e. the sheets labelled 'SEC', 'ETN', 'ADA' etc) if either the biologic-experienced or mixed population is selected (see cells M14, N14 and M21 on the model calculation sheets).

b. Please clarify why the results reported in Table 84, page 158 of the CS do not match the results reported in decision model Excel file, in the "PSA" tab under the "Projected Incremental Costs and QALYs" headline.

Response: The results reported in Table 84 of the company submission are the total costs and QALYs for each comparator, with incremental costs and QALYs reported compared with conventional care. The results presented under the "Projected

[d] Note that this is not the case when the NMA approach is selected to be "PREVENT data only (no NMA)" on the "Settings" sheet.

Incremental Costs and QALYs" on the 'PSA' sheet report incremental results for secukinumab versus each possible comparator (i.e. secukinumab vs. certolizumab pegol, secukinumab vs. etanercept, etc). The results presented in Table 84 can be found in columns IB to IQ of the 'PSA' sheet.

B11. Please clarify what the “Placeholder” scenarios in the “Settings” tab at the “Load/Modify scenarios” option of the decision model represent and how they can be used.

Response: The “Load/Modify scenarios” feature allows the user to specify and store multiple model scenarios by using the existing “Placeholder” options. Once the scenarios have been stored and saved, the corresponding results can be loaded using the “Load scenario” option of this feature.

- To add and/or modify a scenario:
    - Select and apply the desired inputs on the ‘Settings’ sheet to run a particular scenario
      (Note: inputs on the ‘Mortality’ and ‘Efficacy’ sheets can’t be altered)
    - Click “Load/Modify scenarios” on the “Settings” sheet
    - Select the “Add or modify existing scenario” tab
    - Select “Placeholder 1” from the drop-down list
    - Include a description of the scenario applied in the blank field
    - Click on the “Click to modify the selected scenario with current model values” button
    - Re-name the specified scenario by answering “Yes” to the pop-up, if desired

- To load a scenario:
    - Click “Load/Modify scenarios” on the “Settings” sheet
    - Select the “Load scenario” tab
    - Select the saved scenario from the drop-down list
    - Click the “Click to load selected scenario” button

- To delete a scenario:
    - Click “Load/Modify scenarios” on the “Settings” sheet
    - Select the “Delete existing scenario” tab
    - Select the scenario to be deleted from the drop-down list
    - Click the “Click to delete an existing scenario” button

B12. The submitted economic model does not allow for a response criterion other than BASDAI50 to be chosen in cell D33 of the "Settings" tab. If feasible, please provide an Excel model file that allows implementing the ASAS40 response criteria scenario.

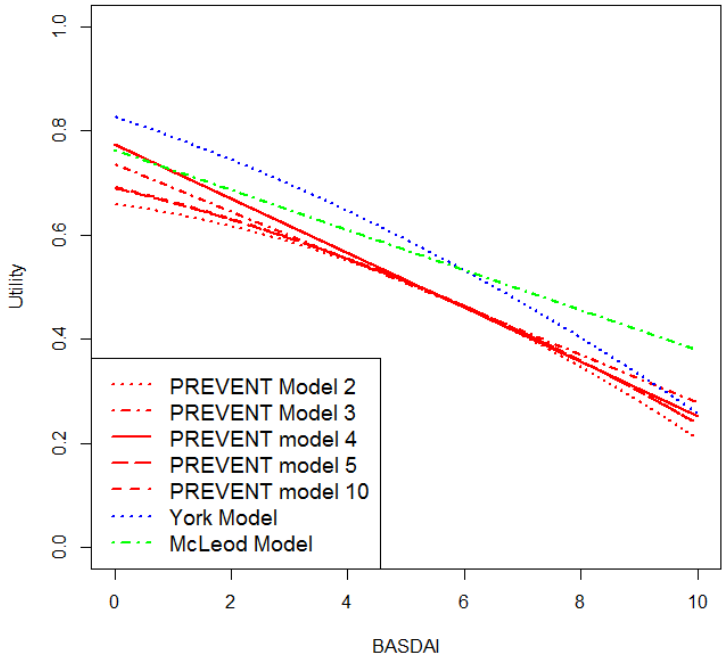
Response: In the base-case, the NMA selection (i.e. the TNFα inhibitor exchangeable joint correlated BASDAI50, BASDAI change from baseline and BASFI change from baseline scenario) only allows BASDAI50 as the response criteria. This is the case in all NMA models which include BASDAI50 as a parameter. ASAS40 may be applied as response criteria with uncorrelated NMA models only.

Other questions

B13. Please provide Figures 3 and 4 of the "ICON 2019" document in the references, which illustrate the predicted EQ-5D values based on different utility mapping algorithms, adding models 2, 3 and 5 based on the PREVENT trial data. Please also provide Tables 2, 3 and 4 of the same document showing the 10th and 90th quantiles.

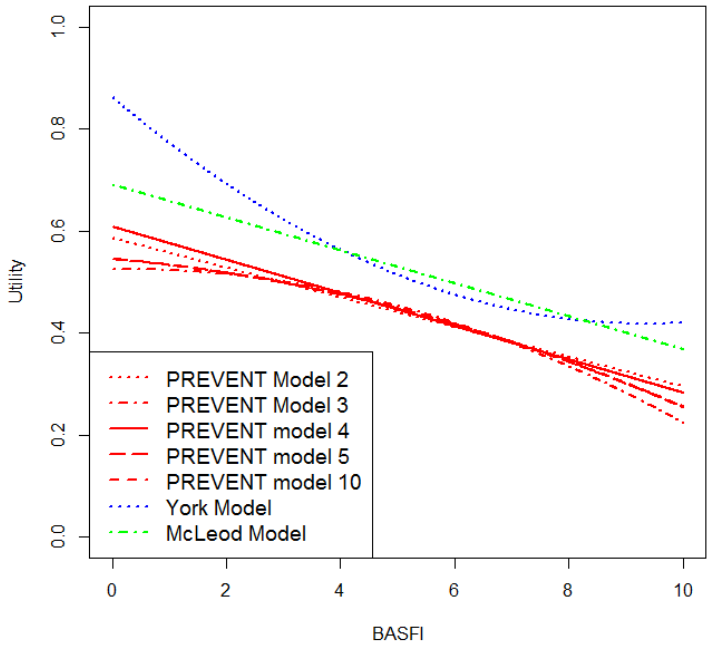
Response: Updated figures and tables are presented below.

Figure 6: Illustration of predicted EQ-5D utility values using different mapping algorithms: constant BASFI and varying BASDAI



Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

Figure 7: Illustration of predicted EQ-5D utility values using different mapping algorithms: constant BASDAI and varying BASFI



Abbreviations: Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

Table 42: Descriptive statistics for BASDAI, BASFI and EQ-5D utility score in the PREVENT trial – overall and by visit

Instrument	Visit	n	Mean	SD	Median	Min	Max	q1	q3	10th quant.	90th quant.
BASDAI	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASFI	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D utility	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Overall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; SD, standard deviation.

Table 43: Descriptive statistics for BASDAI, BASFI and EQ-5D utility score in the MEASURE1/2 trials – overall and by visit

Instrument	Visit	n	Mean	SD	Median	Min	Max	q1	q3	10th quant.	90th quant.
BASDAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASFI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; SD, standard deviation.

Table 44: Descriptive statistics for BASDAI, BASFI and EQ-5D utility score in the sample of pooled PREVENT and MEASURE1/2 trial data – overall and by visit

Instrument	Visit	n	Mean	SD	Median	Min	Max	q1	q3	10th quant.	90th quant.
BASDAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASFI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

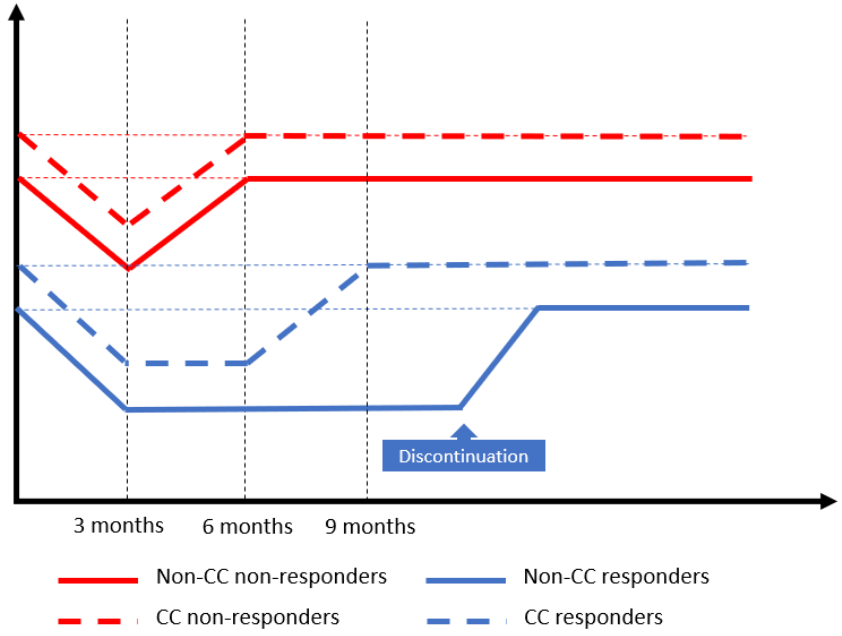
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; SD, standard deviation.

B14. Please provide a description of Figures 26 and 27, page 132 in the CS, explaining in detail the assumptions that relate to the BASDAI and BASFI trajectories

Response: Figures 26 and 27 from the company submission are reproduced in Figure 8 and Figure 9 below, respectively. The tracking of BASDAI and BASFI scores throughout the induction, maintenance and post-discontinuation treatment phases is summarised in Table 62 of the company submission.

BASDAI:

Figure 8: Illustrative change in BASDAI over time†



Abbreviations: CC, conventional care; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.
†The presented scenario reflects the base-case in which initial gain is reversed following non-response or subsequent discontinuation. Diagrams are for illustrative purposes and are not drawn to scale.

Changes in BASDAI over time are as follows:

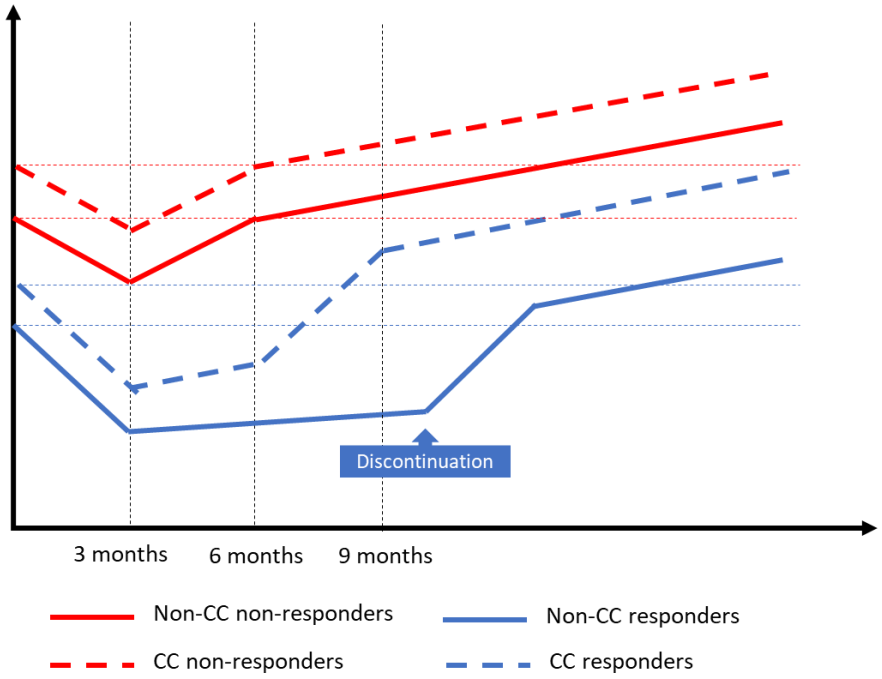
- At 3 months, all patients experience a change in BASDAI from baseline that is specific to treatment type and response status
- For non-responders, this initial change is reversed at 6 months, and BASDAI then remains constant over time

- For responders to biologic treatment, this initial change is maintained until discontinuation; upon discontinuation, the initial change is reversed and BASDAI then remains constant over time

    - For responders to conventional care, the initial change is assumed to be maintained for only one 3-month cycle; following one cycle, the initial change is reversed and BASDAI then remains constant over time

BASFI:

Figure 9: Illustrative change in BASFI over time† (Initial gain)



Abbreviations: CC, conventional care; BASFI, Bath Ankylosing Spondylitis Functional Index.
†The presented scenario reflects the base-case in which initial gain is reversed following non-response or subsequent discontinuation. Diagrams are for illustrative purposes and are not drawn to scale.

Changes in BASFI over time are as follows:

- At 3 months, all patients experience a change in BASFI from baseline that is specific to treatment type and response status

- For non-responders, this initial change is reversed at 6 months, and BASFI then increases at a CC-specific rate over time

- For responders to biologic treatment, BASFI increases from the point of the initial change at a biologic-specific rate until discontinuation; upon discontinuation, the initial change is reversed and BASFI then increases at a CC-specific rate over time

    - For responders to conventional care, BASFI increases from the point of the initial change at a CC-specific rate for only one 3-month cycle; following one cycle, the initial change is reversed and BASFI then increases at a CC-specific rate over time

B15. Please confirm if the PAS [page 16 of CS] is the PAS for secukinumab to treat AS, and that this is intended to be carried over to nr-AxSpA.

Response:

[redacted]

Section C: Textual clarification and additional points

C1. PRIORITY. Please provide the full EPAR document.

Response: The EPAR is provided in the reference pack. Note that this covers the existing indication and not nr-axSpA as marketing authorisation has not yet been granted [23].

C2. In the “Sample size and power calculation” section of the CS (page 47), the company briefly mentions “a meta-analysis from studies with secukinumab studies in AS”. Could the company please provide the relevant reference?

Response: The studies referred to are the MEASURE 3 [24] and MEASURE 4 [25] trials. Both studies are published, but not a combination of them. The meta-analysis was the combination of the placebo response of the two studies.

C3. In Table 9, page 41 of the CS – should the bottom row read ‘experienced’ rather than ‘naïve’? Please provide further details about the TNF-experienced patients i.e.

the number of patients who had no response, lost their response or were intolerant to their anti-TNF.

Response: Correct – in the CS this table should read ‘experienced’ rather than ‘naïve’. Regarding TNF-experienced patients, during enrolment, clinicians screened patients and ensured that each fulfilled any of the IR (insufficient response) criteria. In order to be eligible for inclusion, patients who had been on a TNF-alpha inhibitor (not more than one) had to have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to randomization or had been intolerant to at least one administration of an anti-TNF-alpha agent.

While these data were collected at each study centre, they were not transferred to the central database and so further details are not available.

C4. Page 105 of the CS says

“[redacted] (79)” but reference 79 is about the safety of secukinumab – is this the correct reference?

Response: This is not the correct reference. The reference for this statement is Robinson et al, 2019 [26].

References

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9. Brown, M.A., et al., *Evaluation of the effect of baseline MRI sacroiliitis and C reactive protein status on etanercept treatment response in non-radiographic axial spondyloarthritis: a post hoc analysis of the EMBARK study.* Ann Rheum Dis, 2018. **77**(7): p. 1091-1093.
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15. The Regional Medicines Optimisation Committee (South), *Regional Medicines Optimisation Committee (RMOC) Advisory Statement: Sequential Use of Biologic Medicines. Available at: https://www.sps.nhs.uk/articles/rmoc-advisory-statement-sequential-use-of-biologic-medicines/ (last accessed 27 Jan 2020).* 2020.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Secukinumab for treating non-radiographic axial spondyloarthritis [ID1419]

Addendum to clarification questions

February 2020

File name	Version	Contains confidential information	Date
ID1419 Secukinumab Company answers to ERG clarification 4th Feb updates_FINAL	**1**	**Yes ([redacted] and [redacted])**	**04/02/20**

Section B: Clarification on cost-effectiveness data

Cost effectiveness in general

B1. PRIORITY. As per questions A17 and A20, could the company please re-run all cost effectiveness analyses using NMA results where the load and non-load arms in the PREVENT trial are combined?

Response: As discussed in the previous response to Question A17, we do not consider it appropriate to pool results from the Load and No Load arms; however, a scenario analysis is provided in which the company submission base-case is updated using the analysis described in Question A17 (i.e. simple arithmetic pooling)[a]. The results of this scenario are presented in Table 1 (biologic-naïve population) and Table 2 (biologic-experienced population).

Table 1: Deterministic results based on combined Load and No Load data for secukinumab (biologic-naïve population)

Treatment	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER vs. baseline	ICER (fully incremental)
Conventional care	[redacted]	[redacted]	-	-	-	-
Adalimumab biosimilar	[redacted]	[redacted]	£8,181	1.49	£5,491	£5,491
Secukinumab	[redacted]	[redacted]	£8,265	1.06	£7,797	Dominated
Etanercept biosimilar	[redacted]	[redacted]	£26,734	1.41	£18,960	Dominated
Etanercept	[redacted]	[redacted]	£29,950	1.41	£21,241	Dominated
Certolizumab pegol	[redacted]	[redacted]	£30,521	1.64	£18,610	£148,933
Adalimumab	[redacted]	[redacted]	£32,754	1.49	£21,983	Dominated
Golimumab	[redacted]	[redacted]	£33,023	1.65	£20,014	£250,200

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 2: Deterministic results based on combined Load and No Load data for secukinumab (biologic-experienced population)

Treatment	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER vs. baseline	ICER (fully incremental)
Conventional care	[redacted]	[redacted]	-	-	-	-
Secukinumab	[redacted]	[redacted]	-£8,854	0.86	Dominant	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

[a] Note that analyses based on the pooled dose are not available for all scenarios in the electronic model. Note also that the standard errors for the overall baseline BASDAI and BASFI are not available for the pooled analysis; it has therefore been assumed that these standard errors are equal to the average of the standard errors for secukinumab (loading dose) and placebo.

B2. PRIORITY. The supplied economic model uses the shrunken estimates from the class effect NMA model to inform the effectiveness of the different TNFα inhibitors. Could the company please re-evaluate cost-effectiveness using the predictive distribution of the class-effect to represent a single effect estimate for TNFα inhibitors (as was done in the MTA [TA383])? This will entail simplifying the economic model to consider only one TNFα inhibitor comparator (to represent the class) whose cost is based on the 'mixed-basket' approach (excluding secukinumab). Please use the pooled evidence from load and no-load arms of the PREVENT trial (as requested in B1).

Response: A response to Question B2 has been provided previously; this response has been updated to use the pooled analysis based on data from the Load and No Load arms of PREVENT (see Question B1). Efficacy data used in this scenario are presented in Table 3.

The results of this scenario are presented in Table 4. Secukinumab is shown to be a highly cost-effective treatment option.

Table 3: Efficacy data used in scenario analysis (combined Load and No Load data)

Treatment	BASDAI 50	Baseline BASDAI		Baseline BASFI		BASDAI change from baseline		BASFI change from baseline	
		R	NR	R	NR	R	NR	R	NR
CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TNFα inhibitor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care; NR, non-responder; R, responder; TNFα, Tumour necrosis factor alpha.

Table 4: Results of scenario analysis (combined Load and No Load data)

Treatment	Total costs	Total QALYs	Incremental costs vs. CC	Incremental QALYs vs. CC	ICER vs. CC	ICER (fully incremental)
CC	[redacted]	[redacted]	-	-	-	-
Secukinumab	[redacted]	[redacted]	£8,265	1.06	£7,797	£7,797
TNFα inhibitor	[redacted]	[redacted]	£21,355	1.58	£13,516	£25,173

Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TNFα, Tumour necrosis factor alpha.

B4. PRIORITY. Could the company please re-evaluate cost-effectiveness by comparing the following treatment sequencing scenarios:

a. Secukinumab in first line, followed by a TNFα inhibitor in 2nd-line,

b. TNFα inhibitor in first line followed by secukinumab in 2nd-line,

c. TNFα inhibitor in first line followed by another TNFα inhibitor in 2nd-line.

Please use the pooled evidence from load and no-load arms of the PREVENT trial (as in B1) and a single effect estimate for TNFα inhibitors (as in B2). Assume that 100% of patients move to 2nd-line. Please identify and use evidence from trials and/or registries relating to the reduction in efficacy of TNFα inhibitors in 2nd-line. Please reproduce and report all scenario and sensitivity analyses. Consider alternative scenarios where the treatment effect of secukinumab is i) maintained and ii) reduced at 2nd-line.

Response: A response to Question B4 has been provided previously; this response has been updated:

1. to use the pooled analysis based on data from the Load and No Load arms of PREVENT (see Questions B1 and B2); and

2. to provide univariate and probabilistic sensitivity analysis for this updated scenario.

Base-case results are presented assuming each of the following:

- The treatment effect for both secukinumab and TNFα inhibitors is reduced at second line (see Table 5)

- The secukinumab treatment effect is maintained at second line; a reduction is applied for TNFα inhibitors (see Table 6).

As noted in our previous response, the requested analysis is considered to be subject to substantial uncertainty (see Page 35 of initial response).

In all sensitivity analyses, the treatment effect at second line is assumed to be reduced for both secukinumab and TNFα inhibitors.

The results of probabilistic sensitivity analysis are presented in Table 7, Figure 1, Figure 2 and Figure 3. The results of univariate sensitivity analysis are presented in Figure 4 and Figure 5. The results of scenario analysis are presented in Table 8.

Table 5: Base-case results (secukinumab treatment effect reduced at second line; combined Load and No Load data)

Treatment pathway	Total costs	Total QALYs	Incremental costs vs. baseline†	Incremental QALYs vs. baseline†	ICER vs. baseline†	ICER (fully incremental)
Secukinumab -> TNFα inhibitor	[redacted]	[redacted]	-	-	-	-
TNFα inhibitor -> TNFα inhibitor	[redacted]	[redacted]	£8,485	0.55	£15,427	£15,427
TNFα inhibitor -> secukinumab	[redacted]	[redacted]	£13,785	0.16	£86,156	Dominated

Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TNFα, Tumour necrosis factor alpha.
† The baseline is secukinumab -> TNFα inhibitor.

Table 6: Base-case results (secukinumab treatment effect maintained at second line; combined Load and No Load data)

Treatment pathway	Total costs	Total QALYs	Incremental costs vs. baseline†	Incremental QALYs vs. baseline†	ICER vs. baseline†	ICER (fully incremental)
Secukinumab -> TNFα inhibitor	[redacted]	[redacted]	-	-	-	-
TNFα inhibitor -> TNFα inhibitor	[redacted]	[redacted]	£8,485	0.55	£15,427	£15,427
TNFα inhibitor -> secukinumab	[redacted]	[redacted]	£14,233	0.71	£20,046	£35,925

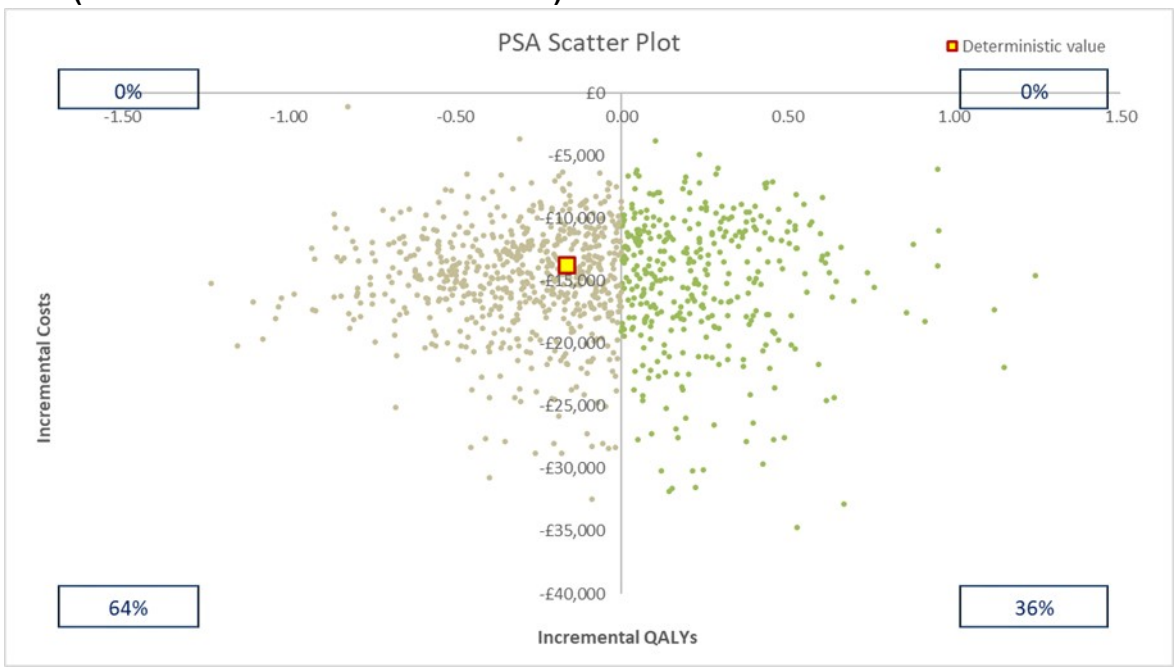
Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TNFα, Tumour necrosis factor alpha.
† The baseline is secukinumab -> TNFα inhibitor.

Table 7: Results of probabilistic sensitivity analysis (combined Load and No Load data)

Treatment pathway	Total costs	Total QALYs	Incremental costs vs. baseline†	Incremental QALYs vs. baseline†	ICER vs. baseline†	ICER (fully incremental)
Secukinumab -> TNFα inhibitor	[redacted]	[redacted]				
TNFα inhibitor -> TNFα inhibitor	[redacted]	[redacted]	£9,283	0.48	£19,340	£19,340
TNFα inhibitor -> secukinumab	[redacted]	[redacted]	£14,928	0.11	£135,709	Dominated

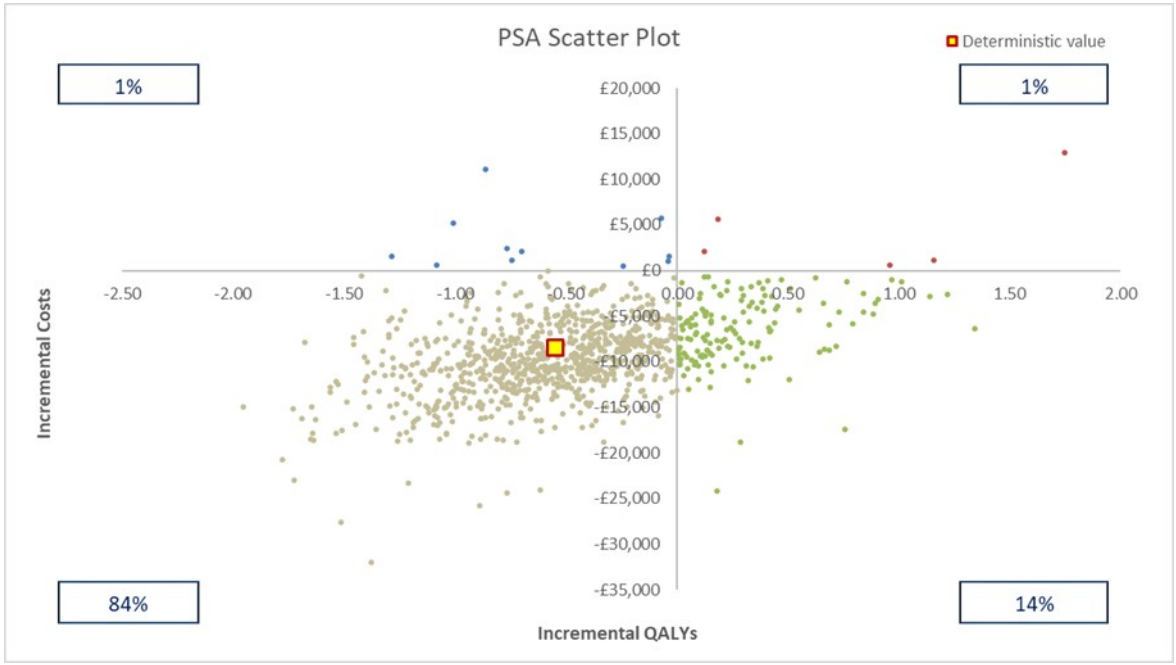
Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TNFα, Tumour necrosis factor alpha.
† The baseline is secukinumab -> TNFα inhibitor.

Figure 1: Scatter plot of PSA results: SEC-> TNFα inhibitor versus TNFα inhibitor -> SEC (combined Load and No Load data)



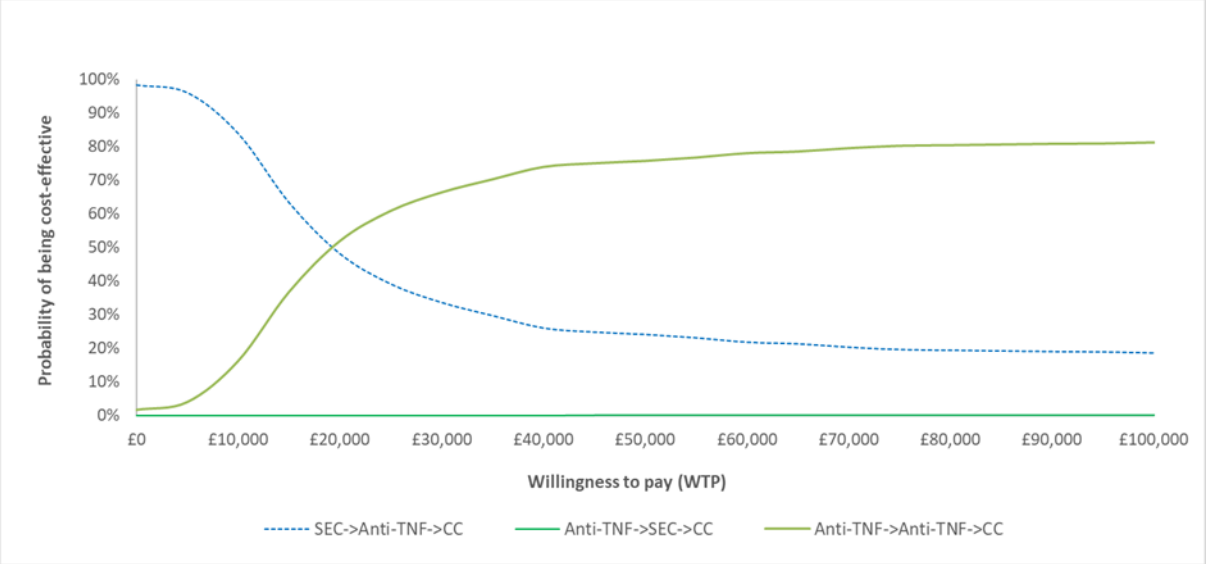
Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SEC, secukinumab; TNFα, tumour necrosis factor alpha.

Figure 2: Scatter plot of PSA results: SEC-> TNFα inhibitor versus TNFα inhibitor -> TNFα inhibitor (combined Load and No Load data)



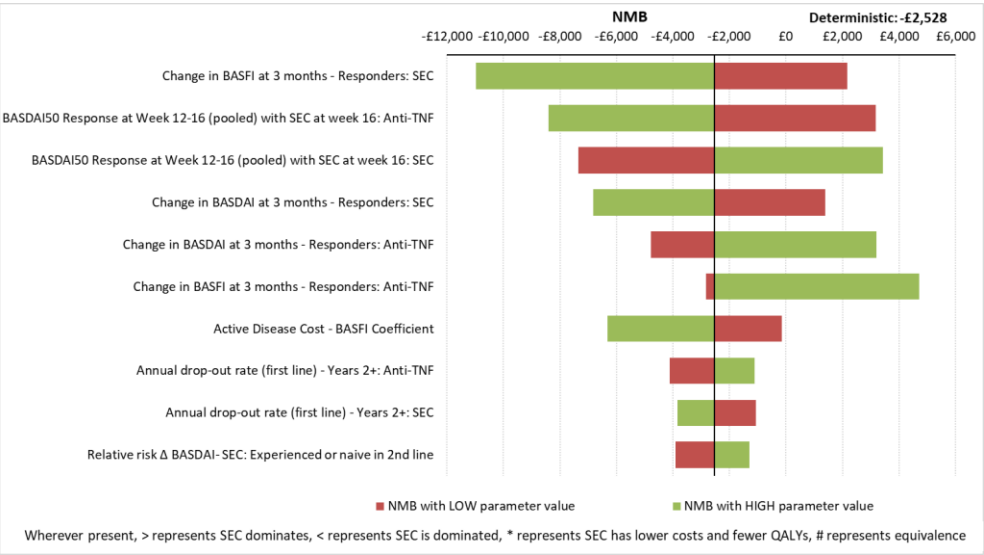
Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SEC, secukinumab; TNFα, Tumour necrosis factor alpha.

Figure 3: Multiple CEAC (combined Load and No Load data)



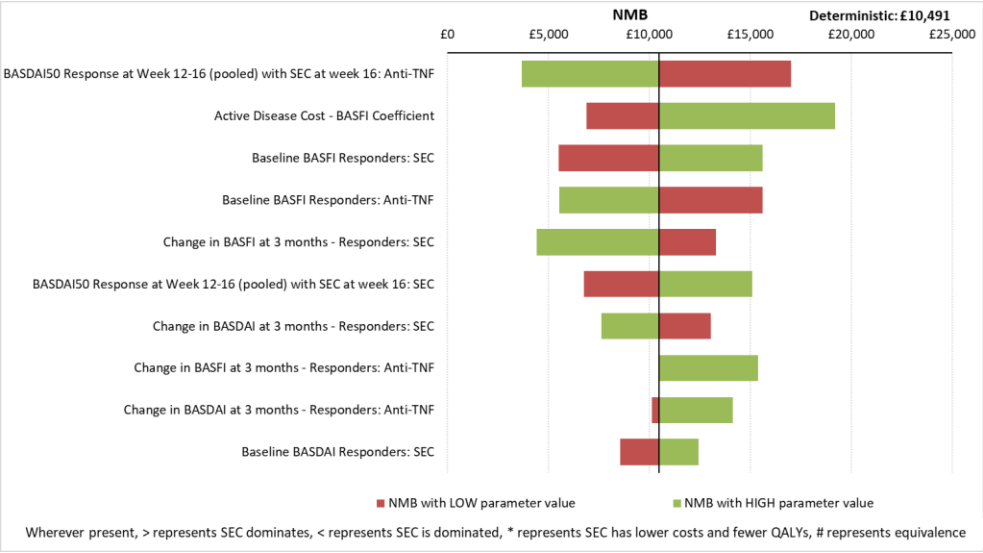
Abbreviations: CC, conventional care; CEAC, cost-effectiveness acceptability curve; SEC, secukinumab; TNFα, Tumour necrosis factor alpha.

Figure 4: Tornado diagram: SEC -> TNFα inhibitor versus TNFα inhibitor -> TNFα inhibitor (combined Load and No Load data)



Abbreviations: BASDAI, Bath Ankylosing Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care; NMB, Net Monetary Benefit; RR, rate ratio; SEC, secukinumab.

Figure 5: Tornado diagram: SEC -> TNFα inhibitor versus TNFα inhibitor -> SEC (combined Load and No Load data)



Abbreviations: BASDAI, Bath Ankylosing Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care; NMB, Net Monetary Benefit; RR, rate ratio; SEC, secukinumab.

Table 8: Results of scenario analysis (combined Load and No Load data)

Area of uncertainty	Base case	Scenario	ICER for secukinumab -> TNFα inhibitor	
			vs. TNFα inhibitor -> secukinumab	vs. TNFα inhibitor -> TNFα inhibitor
Time horizon	Lifetime (maximum age of 100 years)	5 years	£ 22,475*	£11,120*
		10 years	£31,326*	£14,382*
		20 years	£46,118*	£15,519*
		40 years	£75,953*	£15,479*
Discounting	3.5% for costs and outcomes	No discounting	£235,610*	£15,678*
		3.5% for costs, 1.5% for outcomes	£93,575*	£12,402*
Impact on BASDAI and BASFI following discontinuation	Reverse initial gain	Revert to natural history	£86,596*	£15,768*
Biologic-specific treatment effect on BASFI	Treatment effect implemented from beginning of maintenance treatment	Treatment effect implemented after 4 years	£84,554*	£15,510*
		No treatment effect	£86,192*	£15,784*
Utility model	Based on PREVENT	Model used by the assessment group for TA383	£53,634*	£12,942*
		Based on pooled PREVENT and MEASURE 1/2 data	£135,888*	£14,835*
		Model presented in McLeod et al	£59,376*	£11,749*
AE disutilities	Excluded	Included	£ 83,704*	£ 15,409*

*South-west quadrant.
Abbreviations: AE, adverse event; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

Scenario analyses and subgroups

B5. PRIORITY. Please provide a scenario analysis (using the model and comparisons in B4) that assumes common baselines for responders and non-responders. Please justify the baseline values used.

Response: A response to Question B5 has been provided previously; this response has been updated to use the pooled analysis based on data from the Load and No Load arms of PREVENT (see Questions B1, B2 and B4).

The results of this scenario are presented in Table 9.

Table 9: Results of scenario analysis

	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER vs. baseline	ICER (fully incremental)
Submitted base-case model						
Conventional care	[redacted]	[redacted]	-	-	-	-
Adalimumab biosimilar	[redacted]	[redacted]	£3,158	1.59	£1,986	£1,986
Secukinumab	[redacted]	[redacted]	£7,217	1.1	£6,561	Dominated
Etanercept biosimilar	[redacted]	[redacted]	£23,911	1.48	£16,156	Dominated
Etanercept	[redacted]	[redacted]	£27,127	1.48	£18,329	Dominated
Certolizumab pegol	[redacted]	[redacted]	£27,437	1.72	£15,952	£186,762
Adalimumab	[redacted]	[redacted]	£27,730	1.59	£17,440	Dominated
Golimumab	[redacted]	[redacted]	£29,948	1.73	£17,311	£251,100
Sequencing model (reduced efficacy at second line for secukinumab and TNFα inhibitors)						
Secukinumab -> TNFα inhibitor	[redacted]	[redacted]	-	-	-	-
TNFα inhibitor -> secukinumab	[redacted]	[redacted]	£4,342	0.39	£11,133	£11,133
TNFα inhibitor -> TNFα inhibitor	[redacted]	[redacted]	£8,198	0.57	£14,382	£21,422
Sequencing model (reduced efficacy at second line for TNFα inhibitors only)						
Secukinumab -> TNFα inhibitor	[redacted]	[redacted]	-	-	-	-
TNFα inhibitor -> secukinumab	[redacted]	[redacted]	£4,322	0.95	£4,549	£4,549
TNFα inhibitor -> TNFα inhibitor	[redacted]	[redacted]	£8,198	0.57	£14,382	Dominated

Abbreviations: CC, conventional care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TNFα, Tumour necrosis factor alpha.

B6. PRIORITY. Given the concerns as to whether secukinumab is effective in patients who are MRI or CRP negative (Question A16 and A21), could the company please re-run the cost effectiveness analysis for the subgroups defined by MRI and

CRP status (MRI+/CPR+ vs. MRI+/CRP- vs. MRI-/CRP+) and in the subgroups defined by MRI (MRI+ vs MRI-).

Response: The required data are not available for these subgroups for TNFα inhibitors[b]; it is therefore only possible to present a comparison between secukinumab and conventional care based on subgroup data from PREVENT. These analyses are therefore not a suitable basis to inform choice of biologic in subgroups defined by MRI+ and/or CRP+. Evidence in ankylosing spondylitis (AS) suggests that TNFα inhibitors may also be less effective in patients with lower CRP levels (2); in a post-hoc analysis of etanercept trials in AS, very high baseline CRP was a significant predictor of 12-week outcomes (3).

As discussed previously, a simple approach to this analysis has been performed based on the mixed population (i.e. both the biologic-naïve and biologic-experienced populations); subgroup data are only available for the mixed population from the PREVENT clinical study report.

No subgroup data are currently available for:

- baseline BASDAI and BASFI
- change from baseline in BASDAI and BASFI for responders and non-responders separately.

The following assumptions were therefore made:

- Baseline BASDAI and BASFI in each of the subgroups is equal to baseline BASDAI and BASFI for the overall population
- Response-specific change from baseline in BASDAI and BASFI in each of the subgroups was calculated as follows:

[b] BASDAI50 data are available for etanercept patients from Brown et al (1); however, this would not be sufficient to populate the cost-effectiveness model..

- Equation 1: Overall change from baseline = Responder change from baseline x % response + Non-responder change from baseline x (1-% response)
- % response and the overall change from baseline for BASDAI and BASFI are available for each subgroup
- The ratio between change from baseline for responders and non-responders was assumed to be the same as that in the overall population
- Equation 1 can then be solved on this basis

The distribution of patients across subgroups is presented in Table 10.

Table 10: Distribution of patients across subgroups in PREVENT

Subgroup	Secukinumab (Load and No Load)	Secukinumab (Load only)	Placebo
CRP+ and MRI+	111	54	55
CRP+ and MRI-	103	52	51
CRP- and MRI+	155	79	80
MRI+	266	133	135
MRI-	103	52	51

Abbreviations: CRP, C-reactive protein; MRI, magnetic resonance imaging.

The results of subgroup analyses are presented in Table 12–Table 16; the results for the overall mixed population are presented in Table 11 for reference.

Table 11: Results for overall mixed population

Treatment	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER vs. baseline
Conventional care	[redacted]	[redacted]	-	-	-
Secukinumab (pooled load and no load)	[redacted]	[redacted]	£11,885	0.85	£13,982
Secukinumab (load only)	[redacted]	[redacted]	£15,264	0.69	£22,122

Abbreviations: CRP, C-reactive protein; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

Table 12: Results of subgroup analysis (CRP+ and MRI+ subgroup of mixed population)

Treatment	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER vs. baseline
Conventional care	[redacted]	[redacted]	-	-	-
Secukinumab (pooled load and no load)	[redacted]	[redacted]	£9,194	1.34	£6,861
Secukinumab (load only)	[redacted]	[redacted]	£12,396	1.23	£10,078

Abbreviations: CRP, C-reactive protein; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

Table 13: Results of subgroup analysis (CRP+ and MRI- subgroup of mixed population)

Treatment	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER vs. baseline
Conventional care	[redacted]	[redacted]	-	-	-
Secukinumab (pooled load and no load)	[redacted]	[redacted]	£13,906	0.51	£27,267
Secukinumab (load only)	[redacted]	[redacted]	£17,584	0.33	£53,285

Abbreviations: CRP, C-reactive protein; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

Table 14: Results of subgroup analysis (CRP- and MRI+ subgroup of mixed population)

Treatment	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER vs. baseline
Conventional care	[redacted]	[redacted]	-	-	-
Secukinumab (pooled load and no load)	[redacted]	[redacted]	£15,045	0.52	£28,933
Secukinumab (load only)	[redacted]	[redacted]	£19,145	0.29	£66,017

Abbreviations: CRP, C-reactive protein; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

Table 15: Results of subgroup analysis (MRI+ subgroup of mixed population)

Treatment	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER vs. baseline
Conventional care	[redacted]	[redacted]	-	-	-
Secukinumab (pooled load and no load)	[redacted]	[redacted]	£12,496	0.86	£14,530
Secukinumab (load only)	[redacted]	[redacted]	£16,214	0.67	£24,200

Abbreviations: ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

Table 16: Results of subgroup analysis (MRI- subgroup of mixed population)

Treatment	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER vs. baseline
Conventional care	[redacted]	[redacted]	-	-	-
Secukinumab (pooled load and no load)	[redacted]	[redacted]	£13,906	0.51	£27,267
Secukinumab (load only)	[redacted]	[redacted]	£17,584	0.33	£53,285

Abbreviations: ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

References

1. Brown MA, Bird PA, Robinson PC, Mease PJ, Bosch FVD, Surian C, et al. Evaluation of the effect of baseline MRI sacroiliitis and C reactive protein status on etanercept treatment response in non-radiographic axial spondyloarthritis: a post hoc analysis of the EMBARK study. Ann Rheum Dis. 2018;77(7):1091-3.
2. Poddubnyy D. Axial spondyloarthritis: is there a treatment of choice? Therapeutic Advances in Musculoskeletal Disease. 2013;5(1):45-54.
3. Baraliakos X, Szumski A, Koenig AS, Jones H. The role of C-reactive protein as a predictor of treatment response in patients with ankylosing spondylitis. Semin Arthritis Rheum. 2019;48(6):997-1004.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Secukinumab for treating non-radiographic axial spondyloarthritis [ID1419]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Spondyloarthritis Special Interest Group (SIG)**
2. Name of organisation	**British Society for Rheumatology**
3. Job title or position	[redacted]

4. Are you (please tick all that apply):	✓ ☐ an employee or representative of a healthcare professional organisation that represents clinicians? ✓ ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**British Society for Rheumatology Spondyloarthritis Special Interest Group (SIG)**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Reduce pain, fatigue improve mobility, improve quality of life, reduce disability and improve productivity.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in spinal pain VAS and BASDAI by at least 2 points. Aim for a significant improvement of outcome scores by >50%
8. In your view, is there an unmet need for patients and	Yes – some patients do not tolerate or respond to other available therapies (NSAIDS and TNF inhibitors). We need an alternative where anti-TNF loses effect or is contra-indicated

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	NSAID, physiotherapy, TNF inhibitors
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE CG 65 Spondyloarthritis in over 16s NICE QS 170
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well-defined with clear national and international guidelines about management. There is variety between centres on the starting anti-TNF allocated to each centre dependent on local commissioning agreements.
• What impact would the technology have on the current pathway of care?	Offer additional therapeutic options to those patients who have not responded to or not tolerated other treatments. Provide an alternative biologic therapy

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes as for radiographic axial SpA
• How does healthcare resource use differ between the technology and current care?	Similar as given subcutaneously
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Current facilities already in use for delivering the technology
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes

• Do you expect the technology to increase length of life more than current care?	Not aware of data about this
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – significant improvements seen in ASQoL in phase 3 studies
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those with non-radiographic AxSpA would benefit as the treatment currently is for radiographic AxSpA only.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	No difference expected, will be used in the same way as for other indications

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Failure to achieve reduction in spinal pain VAS and BASDAI by at least 2 points No additional testing required, routine clinical care
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This is a new mode of action for treatment of non-radiographic axial SpA. It will improve the care for patients with this condition.
• Is the technology a 'step-change' in the management of the condition?	This is a new mode of action for treatment of non-radiographic axial SpA
• Does the use of the technology address any particular unmet need of the patient population?	Extend therapeutic options for patients who do not tolerate or respond to NSAID and TNF inhibitors
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Most common adverse event is infection – usually minor – consistent with safety profile across other indications in previous studies

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – used after failure to respond to at least 2 NSAIDs with positive MRI or elevated CRP
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	ASAS40, BASDAI, BASDAI50, BASFI, health-related quality of life, ASAS PR Yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	
21. How do data on real-world experience compare with the trial data?	Not yet in routine clinical use – limited real world data
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Secukinumab provides a new mode of action for the treatment of non-radiographic axial Spa
- Secukinumab has been shown to improve outcomes in non-radiographic axial Spa
- Secukinumab provides an alternative treatment for patients who have failed anti-TNF in non-radiographic axial Spa
- The efficacy of Secukinumab also encompasses patient reported outcome measures
- The safety of Secukinumab is line with other published data and trials of this agent in axial spondyloarthritis

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Secukinumab for treating non-radiographic axial spondyloarthritis [ID1419]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	National Axial Spondyloarthritis Society (NASS) (formerly National Ankylosing Spondylitis Society)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	NASS is the only charity in the UK solely dedicated to supporting people living with axial spondyloarthritis (axial SpA) including ankylosing spondylitis. We provide information and support to people with the condition, as well as campaigning for better treatment and care. NASS is funded by a variety of voluntary sources including membership, individual fundraisers, charitable trusts, legacies and industry funding. We receive no statutory or government funding. NASS currently has 3,547 members, the majority of which have axial SpA (AS).
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	Yes. **Novartis** £30,000 - Aspiring to Excellence quality improvement programme £11,000 – Part funding for secretariat of All-Party Parliamentary Group for Axial Spondyloarthritis £40,000 – NASS Voices and Members Day (patient information days) **Abbvie** £30,000 - Aspiring to Excellence quality improvement programme **UCB Pharma** £36,250 - Aspiring to Excellence quality improvement programme **Biogen** £60,000 - Aspiring to Excellence quality improvement programme (2 years' funding)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	We conducted a survey of people with axial spondyloarthritis (axial SpA) including ankylosing spondylitis (AS) and their carers which ran from 20 November 2019 to 2 December 2019. We received 330 responses. The questions were based on the questions asked in this submission. 303 valid responses were received with automatic exclusions applied to those who did not live in England and were neither a person living with axial SpA (AS) or a carer of a person with axial SpA (AS).
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Axial Spondyloarthritis (axial SpA) refers to inflammatory disease where the main symptom is back pain, and where the x-ray changes of sacroiliitis *may or may not* be present. Within axial SpA there are two groups: **Ankylosing Spondylitis (AS):** Where the x-ray changes are clearly present. **Non-radiographic axial spondyloarthritis (nr-axSpA):** Where x-ray changes are *not* present but you have symptoms. Around 7 in 10 in this group have visible inflammation which shows on an MRI. 3 in 10 may not have any change visible on the MRI despite symptoms of back pain and other symptoms of inflammatory disease including: • Episodes of uveitis (inflammation in the eyes) • Crohn's disease or ulcerative colitis (inflammatory bowel disease) • Psoriasis • Inflammation in the heel of the foot • Inflammation in the fingers or toes • Elevated markers of inflammation in blood tests • HLA-B27+ Axial SpA is an inflammatory condition of the spine which often produces pain, stiffness, deformity and disability throughout adult life. It is a chronic progressive disease. It is characterised by periods of fluctuating intensity, leading to slowly increasing spinal and peripheral joint damage. The key symptom in early disease is inflammatory back pain (IBP). The onset of back pain and stiffness is usually gradual, being especially severe at night and following immobility. For many people sleep is disturbed, often causing them to get out of bed in the night to move around so as to improve their back pain and stiffness. Pain and stiffness in AS are commonly at their worst first thing in the morning and may improve considerably with stretching and light exercise.

	Persistence of the disease leads to progressive spinal stiffness which may be accompanied by deformity. Up to 25% of people with axial SpA eventually develop complete fusion of the spine which leads to substantial disability and restriction. 50% of people with axial SpA also suffer from associated disorders at sites distant from the spine. In particular, 40% experience episodic eye inflammation (iritis), 16% develop psoriasis and 10% inflammatory bowel disease. Symptoms of axial SpA usually begin in adolescence or early adulthood, a critical period in terms of education, work and establishment of social frameworks and relationships. Symptoms are often present for a long time (7-10 years) before the diagnosis is made. Although most people with axial SpA live a normal lifespan, there is an increased risk of premature death from cardiovascular disease in particular. Since many people with axial SpA are neither deformed nor have peripheral joint abnormalities, much of the burden of living with axial SpA is invisible. The spectrum of severity means that although many people with axial SpA live active and rewarding lives, others experience progressive spinal pain, immobility and functional impairment. Work disability is a major problem with more than 50% of people who are affected suffering work instability. The average age of diagnosis is 24, a prime time for establishing a career. In addition, one-third of people with axial SpA give up work before normal retirement age and another 15% reduce or change their work because of axial SpA. The work capacity of people with axial SpA in the middle decades of life is similar to that of people with rheumatoid arthritis. Being unable to work has important consequences for the individual and his/her family through both loss of earnings and the loss of self-esteem that a career and income provide. People with axial SpA are more likely to be divorced or never to have married and women with axial SpA are less likely to have children. Many people with axial SpA suffer with issues including depression, fatigue and poor sleep during their lives. All of these problems exert a profound influence on their quality of life.

Q11 Describe in your own words what it is like to live with axial spondyloarthritis / ankylosing spondylitis, or what it is like to care for someone with the condition.

Carers commented that they felt frustration at missing out on life and opportunities, but also watching someone young suffer in so much pain left them feeling useless.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	269 people answered this question. Of those 45% believed that current treatments available are sufficient, 55% believed that they are not. When asked why they did not believe the treatment to be sufficient, some common themes did occur: • For some individuals, no medication developed so far has been effective • Some patients may not be able to tolerate any of the current treatments available due to underlying conditions • Efficacy of treatment can wear off over time or it can take a long time to find an effective treatment • Worries about possible side effects • Concerns for patients who do not meet the criteria for biologic therapy but who display severe symptoms We also asked if care was sufficient on the NHS. Of the 269 that answered, 43% believed that it is and 57% that it isn't. The reasons cited for this included: • Insufficient staffing in rheumatology and physiotherapy • A lack of specialist rheumatology physiotherapy • Insufficient knowledge amongst some rheumatologists / a lack of specialist axial SpA (AS) clinics as opposed to general rheumatology clinics • Dwindling access to hydrotherapy • No direct access to help when in a flare • A lack of information on the condition provided when diagnosed and throughout disease course Many of the older patients acknowledged that whilst options for the treatment of axial SpA (AS) had improved, there was still more to be done.
8. Is there an unmet need for patients with this condition?	Those surveyed believed that more research was needed into the causes of axial SpA (AS). Inequalities in care around England also mean that inadequate care is the norm in some areas. In a recent FOI enquiry sent to all NHS Trusts in England, of the 88% of trusts who responded, less than half offered a specialist axial SpA (AS) clinic.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	When asked if they thought that secukinumab should be available for the treatment of non-radiographic axial spondyloarthritis, 88% responded positively. Respondents believed that this would create a 'level playing field' for everyone with the full spectrum of axial SpA (AS), especially as the burden of disease can be as great, if not worse, for those with non-radiographic axial SpA. Others also believed that patients should be given every opportunity to have their symptoms relieved. There is an enthusiasm for anything that may improve the quality of life for those living with the condition, especially if it can be done at an early stage. There is also an opportunity to slow down disease progression if treatment starts at an earlier stage, before a patient has progressed to radiographic changes which are irreversible.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	One patient said that they were no longer able to take this medication as it had affected their mental health. Another questioned if the clinical trials had been robust. One thought the drug was too expensive. People did not feel they had enough technical knowledge to fully comment on the possible disadvantages.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Currently the only biologic drugs available for non-radiographic axial spondyloarthritis (nr-axSpA) are TNF-alpha inhibitors. Any patient who has not responded to this type of drug with nr-axSpA could potentially benefit from this drug, with improved symptoms allowing for a better quality of life. Secukinumab is an IL17-a inhibitor which works differently to TNF-alpha inhibitors and as such could be hugely beneficial to whole new group of patients.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Axial spondyloarthritis is a painful and debilitating condition which can often lead to social isolation at a young age if left untreated.
- All patients within the axial sponyloarthritis deserve the opportunity to the full range of treatment for the condition.
- The technology could significantly improve the quality of life of those with non-radiographic axial spondyloarthritis which has an equal if not greater disease burden than radiographic axial SpA / ankylosing spondylitis.
- There are no other IL17-a biologic drugs currently available for nr-axSpA as an alternative to TNF-alpha inhibitors.
- The vast majority of patients surveyed (88%) would like to see secukinumab available for nr-axSpA.

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Clinical expert statement

Secukinumab for treating non-radiographic axial spondyloarthritis ID1419

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Raj Sengupta**
2. Name of organisation	**Royal National Hospital for Rheumatic Diseases, Bath**

3. Job title or position	**Consultant Rheumatologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Secukinumab is a fully human monoclonal IL-17A antibody of the IgG1/k-class which functions by selectively targeting IL17 as well as other cytokines that play a key role in axial spondyloarthritis (axial SpA). There has been an extensive clinical trial programme with Secukinumab in axial spondyloarthritis (including non radiographic axial SpA) demonstrating the clinical efficacy of this technology. The main aim of this treatment is to reduce the disabling symptoms of this condition which includes stiffness, pain, fatigue, poor sleep. The consequence of this response is better mobility, improved physical function and a significantly improved quality of life for the patient. Secukinumab has also been shown to reduce radiographic progression in patients with axial spondyloarthritis
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A significant treatment response would be an improvement in the BASDAI score by 50% or by at least 2 points. The back pain score has to improve by 2 points.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is an unmet need in axial SpA patients. At present, in the non radiographic axial SpA population, there is only 1 mode of action with biological DMARDs– ie inhibiting TNF. TNF inhibitors are effective treatments but only achieve a meaningful response in approximately 50% of patients. In addition, side effects may be seen in approximately a third of the patients in RCTs. It is important for these patients to have an effective treatment option with an alternative mode of action. Fatigue is a major symptom for most axial spondyloarthritis patients. The fatigue has mental and physical components to it and many patients describe hitting a brick wall with their energy levels. Patients report that

	despite good sleep, the impact of fatigue is very high. There is a variable response to TNF inhibitors where fatigue is concerned. Another unmet need in this population is the delay in diagnosis. The optimal effectiveness of biological DMARDs is evident when the appropriate patients are treated early and often the window of opportunity is missed due to a delay in diagnosis.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	The initial treatment for axial SpA patients remains NSAIDs and physiotherapy. For patients whose symptoms remain uncontrolled, escalation to biological DMARDs is considered if high disease activity scores are recorded and if it is recommended by the treating physician.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines (NG65 and TA383) and BSR guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well defined. Initiation criteria and response criteria are very clear in all axSpA treatment guidelines

• What impact would the technology have on the current pathway of care?	For non radiographic axial SpA patients, choice of biological DMARDs is limited to TNF inhibitors only. Secukinumab should be considered alongside TNF inhibitors as a first line treatment choice. There will be clinical situations where anti IL17 therapy may be more appropriate as 1st line therapy and monthly administration may suit patients. It would give us more choice for patients who do not respond to TNF inhibitors. Presently, an axSpA patients may try 2 anti TNF's which may result in a non response to the drugs – suggesting that TNF may not be the right target with their disease. Anti IL17 inhibition would be an alternative sensible treatment option for these patients.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It would be used in the same way as current care. This technology should be used in line with treatment guidelines for ankylosing spondylitis (radiographic axial spondyloarthritis) patients. In my opinion, this technology should be provided as a 1st or 2nd line choice for axial SpA patients. This technology will be given to axSpA patients who demonstrate high disease activity (BASDAI and back pain score>4), in line with other biological DMARDs used in current clinical practice. In keeping with current NICE guidelines, the least expensive treatment should be used to treat non radiographic axial spondyloarthritis patients.
• How does healthcare resource use differ between the technology and current care?	At present, only TNF inhibitors are available for patients with non radiographic axial SpA. This technology provides an alternative mode of action.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This technology should only be prescribed in secondary care by rheumatologists.
• What investment is needed to introduce the technology? (For	Nil

example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. In patients who have active non radiographic axSpA, this technology will significantly increase health related quality of life. This will be as effective as current anti TNF treatment but is likely to be available for those with side effects to TNF inhibitors. This technology is also particularly effective in axSpA patients with psoriasis.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This treatment should be considered in patients with contraindications to TNF inhibitor therapy – eg multiple sclerosis, TB. The treatment should also be considered in patients with disabling fatigue.

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology will not be any different for patients to use than current care. As clinicians, we are very familiar with the technology in our axial SpA treatment paradigm. The monthly administration is in fact preferred by many of our axSpA patients. Baseline screening (including blood tests and chest xray) will be similar for this technology and in line with routine screening prior to starting other biological DMARDs Training materials for clinicians and patients for this technology are already available.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This will be in line with current NICE guidelines. If the patient's BASDAI score has not improved by at least 50% or 2 points and the back pain score by 2 points when assessed at 16 weeks, the treatment will be stopped. No additional testing is required.

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Nil
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The technology is innovative as it's the first anti IL-17 technology for the use in non radiographic axial SpA patients. These patients have had access to TNF inhibitors only. I have outlined the lack of response to TNF inhibitors in previous questions and this technology provides an alternative treatment for them.
• Is the technology a 'step-change' in the management of the condition?	Yes – as it's the first anti IL17 therapy for this patient group

• Does the use of the technology address any particular unmet need of the patient population?	There are patients who are unable to have anti TNF therapies – those with multiple sclerosis/ family history of multiple sclerosis/ interstitial lung disease. The data for this technology with regard to psoriasis improvement is superior to that seen with TNF inhibitor therapies.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As with other biological DMARDs, adverse and serious adverse events have been seen in clinical trials – however the rates are low. In instances where adverse events occur, the drug is stopped and the patient is switched to an alternative therapy. There were initial concerns regarding the exacerbation of inflammatory bowel disease (IBD). Randomised control trials, post hoc analyses and real world data has not demonstrated a safety signal for IBD in Secukinumab treated patients
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the phase 3 clinical trials for non radiographic axial SpA closely reflect current UK clinical practice.
• If not, how could the results be extrapolated to the UK setting?	N/A

• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important clinical outcomes were BASDAI and back pain score and both were measured in the trials. In addition, radiographic and MRI outcomes were also assessed. Finally adverse events, relevant to clinical practice, were recorded.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the	No

publication of NICE technology appraisal guidance [TAXXX]?	
22. How do data on real-world experience compare with the trial data?	Real world data is mostly comparable to the clinical trials. Our real world Secukinumab study in radiographic axial spondyloarthritis patients showed statistically significant improvements in BASDAI in patients treated with this technology (Williams T, Wadeley A, Bond D, Cavill C, Freeth M, Sengupta R. Real-world experience of secukinumab treatment for ankylosing spondylitis at the Royal National Hospital for Rheumatic Diseases, Bath. Clin Rheumatol. 2020;10.1007/s10067-020-04944-5. doi:10.1007/s10067-020-04944-5. Link)
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	

24. Would secukinumab be considered for patients in the NHS who have a negative MRI scan? As most patients in the UK are diagnosed with non-radiographic axial spondyloarthritis based on a positive MRI, is this a clinically relevant subgroup?	Secukinumab should be considered in all axial SpA patients in line with current NICE TNF inhibitor treatment recommendations.
25. Where is secukinumab most likely to be used in the treatment pathway? Would secukinumab be a treatment option in clinical practice for people when TNFα inhibitors have proven to be ineffective?	Secukinumab should be available for use as 1st and 2nd treatment. Treatment with Secukinumab first line is very effective. It should be also be available as a treatment option where TNF inhibitors have failed given the clinical trials show a very good response to Secukinumab when used in these patients.
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Secukinumab should be available as 1st or 2nd line treatment in non radiographic axial SpA
- Secukinumab should be prescribed in line with current axial SpA treatment guidelines
- Secukinumab efficacy and safety is comparable to existing biological DMARD therapies
- Real world data confirms Secukinumab as an effective treatment in axial SpA
- Quality of life improvements are significant in Secukinumab treated patients

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Secukinumab for treating non-radiographic axial spondyloarthritis ID1419

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.grouo
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Louise Warburton**
2. Name of organisation	**Primary Care rheumatology and MSK Medicine Society and Shropshire Community NHS Trust**

3. Job title or position	**GP with special interest in Rheumatology.**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ **x** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent progression of SpA and to allow treatment of the disease at a very early stage of diagnosis,
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in the Disease activity measurements and functional measurements such as BASDAI. Sorry I do not routinely measure these in my clinical capacity
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, the condition goes unrecognised by GPs and referrers in Primary Care and there is a significant delay in diagnosis
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Referral to a rheumatology service for diagnosis; initially physio and NSAIDs and then Biologic treatmetns if worsening condition
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE SpA Guideline.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Some difference in opinion about diagnosis in the non-radiographic disease and differentiation from other conditions such as fibromyalgia.
• What impact would the technology have on the current pathway of care?	It would allow earlier treatment of this condition and prevent disease progression for patients and improve their outcomes.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes

• How does healthcare resource use differ between the technology and current care?	Currently Secukinumab is not used in non radiographic SpA
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Not much as already in place.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, will improve patient outcomes
• Do you expect the technology to increase length of life more than current care?	Moderately.

• Do you expect the technology to increase health-related quality of life more than current care?	YEs
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	No practical implications; should be as easy to use as currently

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not sure;
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes, treatment will be started earlier in the disease pathway and disease control will be better

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Earlier diagnosis and therefore will improve patient well-being
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Not significantly
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Not sure
• If not, how could the results be extrapolated to the UK setting?	Not sure
• What, in your view, are the most important outcomes, and were they measured in the trials?	Functional outcomes such as BASDAI
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not sure
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not sure
20. Are you aware of any relevant evidence that might	no

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA383, TA407, TA497	no
22. How do data on real-world experience compare with the trial data?	Not sure
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	no

23b. Consider whether these issues are different from issues with current care and why.	n/a
Topic-specific questions	
24. Would secukinumab be considered for patients in the NHS who have a negative MRI scan? As most patients in the UK are diagnosed with non-radiographic axial spondyloarthritis based on a positive MRI, is this a clinically relevant subgroup?	Yes it is; Hard to diagnose and differentiate from fibromyalgia but there is significant disease burden , particularly in women who have Non radiographic SpA.. Use of Secukinumab in this group, judiciously, would be the case.
25. Where is secukinumab most likely to be used in the treatment pathway? Would secukinumab be a treatment option in clinical practice for	Possibly; likely to be first line though before TNFs in patient groups in whom TNF inhibitors are prohibited.

people when TNFα inhibitors have proven to be ineffective?	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- Treatment for SpA which can be used earlier in the treatment pathway
- Earlier treatment prevents long term joint damage
- Patient outcomes will improve with earlier treatment
-
-

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Evidence Review Group's Report

Secukinumab for treating non-radiographic axial spondyloarthritis

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

Authors Georgios Nikolaidis, Research Fellow, CHE

Mark Corbett, Research Fellow, CRD

Sumayya Anwer, Research Fellow, CRD

Susan Griffin, Senior Research Fellow, CHE

Laetitia Schmitt, Research Fellow CHE

Melissa Harden, Information Specialist, CRD

Mark Simmonds, Senior Research Fellow, CRD

Sofia Dias, Professor of Health Technology Assessment, CRD

Marta Soares, Senior Research Fellow, CHE

Correspondence to Marta Soares, Senior Research Fellow, Centre for Health Economics, University of York, Heslington, York, YO10 5DD

Email: marta.soares@york.ac.uk

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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mark Corbett and Sumayya Anwer wrote the clinical effectiveness sections of the report. Mark Simmonds provided advice, commented on drafts of the report and took overall responsibility for the clinical effectiveness sections. Melissa Harden wrote the sections on the search strategies. Georgios Nikolaidis and Marta Soares wrote the cost effectiveness sections and conducted the ERG economic analyses. Susan Griffin provided advice on the cost effectiveness sections and commented on drafts of the report and Laetitia Schmitt critiqued the company's model early in the appraisal. Marta Soares took overall responsibility for the cost effectiveness sections. Sofia Dias provided advice and commented on drafts of the report.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all academic-in-confidence (AIC) data are [redacted], all depersonalised data (DPD) are highlighted in pink and underlined.

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List of abbreviations

ADA adalimumab

AE adverse event

AS ankylosing spondylitis

ASAS Assessment in Ankylosing Spondylitis

ASQoL Ankylosing Spondylitis Quality of Life

axSpA Axial spondyloarthritis

BASDAI Bath Ankylosing Spondylitis Disease Activity Index

BASFI Bath Ankylosing Spondylitis Functional Index

BASMI Bath Ankylosing Spondylitis Metrology Index

BASRI Bath Ankylosing Spondylitis Radiology Index

BNF British National Formulary

BSR British Society for Rheumatology

BSRBR British Society for Rheumatology Biologics Register

CEA cost-effectiveness analysis

CrI Credible interval

CIC commercial in confidence

CMA cost-minimisation analysis

CPI consumer price index

CRD Centre for Reviews and Dissemination

CZP certolizumab pegol

DIC deviance information criterion

DMARD disease-modifying antirheumatic drug

ETA Etanercept

EQ-5D EuroQol 5 Dimensions

GOL Golimumab

HLA human leucocyte antigen

HRQoL health related quality of life

ICER incremental cost-effectiveness ratio

IPD individual patient data

IQR interquartile range

ITT intention-to-treat

MASES Maastricht Ankylosing Spondylitis Enthesitis Score

mSASSS modified Stoke Ankylosing Spondylitis Spinal Score

MTX methotrexate

NA not applicable

NICE National Institute for Health and Clinical Excellence

NR not reported

nr-axSpA Non-radiographic axial spondyloarthritis

NSAID non-steroidal anti-inflammatory drug

OLS ordinary least squares

OR odds ratio

PBO placebo

p.a. per annum

PPP purchasing power parity

PSA probabilistic sensitivity analysis

QALY quality-adjusted life-year

QoL quality of life

RCT randomised controlled trial

RR relative risk

SAE Serious adverse event

SD standard deviation

SEC Secukinumab

SEM standard error of the mean

SF-36 MCS Short Form 36 mental component summary

SF-36 PCS Short Form 36 physical component summary

SIJ Sacroiliac joint

SMR standardised mortality ratio

TB tuberculosis

TNF tumour necrosis factor

VAS visual analogue scale

WMD weighted mean difference

EXECUTIVE SUMMARY

1.1 Critique of the decision problem in the company's submission

The ERG considers that the decision problem presented in the submission matches the NICE scope (see Section 2.4). Briefly, secukinumab (150mg) was the intervention considered, in patients with nr-axSpA with objective signs of inflammation. The ERG notes that how the submission interprets "objective signs of inflammation" could potentially vary slightly from diagnoses made in the NHS. Some outcomes in the NICE scope were not reported, as they were not recorded in the secukinumab trial. Secukinumab was compared to all appropriate alternative therapies (TNFα inhibitors) using a network meta-analysis.

The submission evaluated key patient subgroups; particularly, patients with and without prior exposure to TNFα inhibitors, and according to the nature of the nr-axSpA diagnosis (patients with and without MRI evidence of sacroiliitis and patients with and without elevated CRP levels). The ERG notes that evidence was very limited for the latter subgroups.

1.2 Summary of the key issues in the clinical effectiveness evidence

1.2.1 Clinical effectiveness of secukinumab

Secukinumab was evaluated in a single randomised trial (the PREVENT trial) of 555 patients, divided between secukinumab, given either with or without a loading dose, and placebo. The ERG considers that the trial was generally well conducted and robust, and of sufficient size to detect any effect of secukinumab (see Section 3.2). However, the ERG has some concerns about the trial's generalisability,

[redacted]

1.2.2 Key subgroups

[redacted]The other key subgroups considered in PREVENT were patients with both positive MRI imaging and elevated CRP levels (MRI+/CRP+) compared to those positive for only one of these (MRI+/CRP- and MRI-/CRP+).

[redacted]

[redacted]

1.2.3 Indirect comparison of secukinumab and TNFα inhibitors

Secukinumab was compared to four TNFα inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab) in a network meta-analysis (NMA). The ERG considers that the NMA methodology was appropriate, although limited by the small number of trials and the lack of head-to-head comparisons of treatments (see Section 3.4). The ERG found some data errors in the submitted NMA, which the ERG has sought to correct (Table 8).

[redacted]

[redacted]

1.2.2 Overall summary of clinical effectiveness

Based on the results of PREVENT,

[redacted]

There are concerns about a

[redacted] Also, as it seems that most patients in the UK are diagnosed with nr-axSpA based on a positive MRI scan, there is some uncertainty about how many MRI negative nr-axSpA patients would be considered for treatment with secukinumab.

[redacted]

1.3 Summary of the key issues in the cost effectiveness evidence

The ERG highlights the following key issues relevant to this appraisal, which include not only issues with the evidence presented by the company but also areas of uncertainty surrounding the available evidence:

- There is some uncertainty about the nr-AxSpA population eligible for secukinumab (see item 1). This is due to the large heterogeneity across trials and existing registry information, which in the PREVENT trial (the pivotal study on the effectiveness of secukinumab) manifests itself by a high value of BASFI indicating high functional impairment in the sample recruited and the high and sustained placebo response observed. Additionally, the proposed MA does not limit the use of secukinumab to a particular line of treatment, hence it could be considered at 1st line, at 2nd or 3rd line (where patients may still be considered for TNF inhibitors) and after failing TNF treatment. The manufacturer presents evidence mainly for 1st line use of secukinumab (in line with the available efficacy evidence), but also submits an analysis at 2nd based on a very small subgroup of the PREVENT trial which the ERG deems not to be robust for decision making purposes. No evidence has been submitted on end of line use of secukinumab.
- There is uncertainty about the clinical efficacy results obtained in clinical practice (see item 10), as the response criteria used in clinical practice (i.e. BASDAI50 or a 2-unit change in BASDAI and a reduction in spinal pain VAS by 2 cm or more) is not the one modelled by the company (where BASDAI50 is used in isolation). A recent study[38] highlights that the proportion continuing treatment with TNF under the alternative criteria differs significantly (54.1 vs 80.5%), and hence the implications for cost-effectiveness are expected to be large. However, the company has not submitted evidence from PREVENT using these criteria.
- There is some uncertainty on how to model the disease process (see item 11), particularly in what concerns the use of different baseline BASDAI and BASFI scores across responders and non-responders (i.e. conditional baselines) and on how to consider these differential baselines in modelling subsequent treatments (important to accurately determine cost-effectiveness). The impact of the assumption of conditional baselines on cost-effectiveness can be considerable, but its appropriateness is unclear.

- The cost-effectiveness evidence presented by the manufacturer fails to acknowledge the recent introduction of the adalimumab biosimilar, which is as effective as other TNFα inhibitors and considerably less expensive, and that this treatment is becoming increasingly used for first line treatment (see item 20).
- Additionally, PREVENT data suggests secukinumab's effectiveness may be more comparable to that of TNFα inhibitors in patients that are MRI+, and that the benefit of secukinumab on MRI- patients is very limited.

1.4 Summary of ERG's preferred assumptions and resulting ICER

The ERG has undertaken a number of additional analyses using the evidence and model at hand. Note that the non-sequence model (not considering subsequent treatment with biologics) was used in the base-case with conditional baselines. For the 1st line use of secukinumab, the ERG's base-case, also assumes:

- A single TNFa inhibitor treatment was considered to represent the effectiveness of the class
- TNFα inhibitors were costed according to the adalimumab biosimilar costs
- Baseline BASDAI/BASFI values were sourced from EuroSpA[17] study instead of PREVENT
- Relative effectiveness was estimated using the pooled load and no-load arms of PREVENT trial, which showed comparable clinical results at 16 weeks
- The York utility algorithm that was developed in TA 383 was preferred over the utility model that was using PREVENT data.

The resulting ICER, as shown in [redacted] 25, of TNFα inhibitors compared to secukinumab is [redacted] per QALY gained rendering TNFα inhibitors cost-effective compared to SEC under usual threshold values.

The ERG has also tentatively explored the use of secukinumab in 2nd line, under the following assumptions:

- A single TNF comparator was used that represents the effectiveness of the class, with costs based on etanercept biosimilar (the second cheapest alternative after adalimumab's biosimilar)
- The effectiveness for second line can be reasonably approximated by reducing the first line effectiveness results according to evidence from the DANBIO registry[51]
- The overall BASFI baseline is that of the non-responders to TNFα inhibitors in 1st line inflated by the expected progression in BASFI that has incurred during treatment in 1st line

In second line, the resulting ICER, shown in [redacted], of TNFα inhibitors compared to secukinumab is [redacted] per QALY.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

For the 1st line use of secukinumab the ERG undertook the following sensitivity analyses:

- Sustained placebo response until week 52 or indefinitely
- Common baseline BASDAI/BASFI scores across responders and non-responders
- Costing secukinumab based on the regimen without loading
- Assuming that there is no BASFI progression and effectively that nr-axSpA patients do not progress to AS
- Costing TNFs based on the company's submitted market share data
- Including the costs and effects of subsequent biologic treatment after 1st line use of secukinumab and TNFs, using the company's sequence model under common baselines

Results were generally robust to sensitivity analyses with most scenarios producing ICERs below £10,000 per QALY gained, suggesting that using TNFα inhibitors may be cost-effective compared to secukinumab at 1st line at usual threshold values (See [redacted]26). The key determinant of cost-effectiveness is the cost of TNFa treatment. Considering subsequent treatments was also important to determine cost-effectiveness, but under common baselines the ICER was under threshold values acceptable for policy. It's impact on a model using conditional baselines is unknown.

For the 2nd line use of secukinumab the ERG undertook the following sensitivity analyses:

- Using higher or lower BASFI overall baselines for patients initiating 2nd line therapy
- Using common baseline BASDAI/BASFI scores across responders and non-responders
- Costing the 2nd line TNFα inhibitor based on the most expensive TNFα inhibitor (Golimumab), on the company's market share data, or based on the adalimumab biosimilar
- Informing reduction in effectiveness at 2nd line based on PREVENT

Results were generally robust across all scenarios that assumed that the adalimumab biosimilar is not available in 2nd line, suggesting that secukinumab may be cost-effective at 2nd line compared to TNFα inhibitors ([redacted]27). The scenario which assumed that the adalimumab biosimilar has not been used in 1st line and is therefore available in 2nd line suggests that TNFα inhibitors dominate secukinumab at 2nd line.

2 BACKGROUND

2.1 Description of the health problem

Axial spondyloarthritis (axSpA) - an umbrella term encompassing both non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS) - is a chronic inflammatory arthritis in which back pain is the main symptom. In AS (sometimes referred to as radiographic axial spondyloarthritis or r-axSpA) definitive damage is visible on plain radiographs of the sacroiliac joints (which link the pelvis to the lower spine). In nr-axSpA such damage is not visible on plain X-rays, although inflammation may be visible on an MRI (magnetic resonance imaging) scan, or other symptoms will be evident.[1] The advent of MRI was important as it enabled earlier detection, and therefore earlier treatment, of axSpA, since joint damage may not become evident on radiography for many years.

The Assessment of SpondyloArthritis International (ASAS) Society criteria uses imaging or clinical arms to classify axSpA. All patients must have developed chronic back pain (of at least 3 months duration) before age 45 years. The imaging arm of the ASAS criteria requires evidence of joint

damage (erosions or fusion) due to sacroiliitis (inflammation of a sacroiliac joint), using either radiography (AS classification) or MRI (nr-axSpA classification). In addition to this, at least one of the following Spondyloarthritis (SpA) features is also required: inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's/colitis, good response to non-steroidal anti-inflammatory drugs (NSAIDs), family history of SpA, human leucocyte antigen (HLA)-B27 genetic marker, or elevated C-reactive protein (CRP). To be classified as nr-axSpA via the clinical arm of the criteria, patients must test positive for the HLA-B27 genetic marker and also have at least three of the aforementioned SpA features.[2]

Although there have long been concerns about the clinical arm of the ASAS criteria, regarding its low specificity (given the high prevalence of chronic non-specific back pain), questions have also been raised about the specificity of the current "positive MRI" definition for sacroiliitis according to the ASAS criteria (i.e. the imaging arm may not be as specific as previously thought).[3, 4] The ERG's clinical adviser indicated that in the NHS it is likely that few patients are diagnosed via the clinical arm of the ASAS criteria.

2.1.1 Aetiology, pathology and prognosis

The pathogenesis of nr-axSpA is not yet fully understood. The underlying mechanisms of disease are thought to be autoimmune and autoinflammatory, with the major mediators being the pro-inflammatory cytokines tumour necrosis factor (TNF)-α and interleukin (IL)-17A. Genetics plays a role in the development of nr-axSpA, especially the HLA-B27 allele, though its presence is not essential.

Progression of nr-axSpa is difficult to predict. A review of studies reporting on radiographic progression (to AS) in nr-axSpa patients reported wide variation in estimates. Of the larger studies (n>100) which used ASAS criteria, progression rates seemed correlated with follow up duration: 2% (2 years), 5% (4.4 years), 5.1% (5 years), 8% (8 years) and 10% (11 years).[5] This suggests that the classification criteria for nr-axSpA identifies many patients who are unlikely to progress to AS, though studies with longer follow-up periods are needed to estimate the proportion of patients in this subgroup.

2.1.2 Epidemiology

Whilst AS is more common in men (70-80% of the population) than in women, in the nr-axSpA population the distribution is more even, with between 48% and 64% being male.[6, 7] Despite age differences, nr-axSpA patients have similar comorbidity burdens as AS patients; in a U.S. study comparing nr-axSpa (n=134) with AS patients (n=641) the mean number of comorbidities was similar (around 1.5).[7]

2.1.3 Incidence/prevalence

A systematic review of the incidence and prevalence of axSpA, published in 2018, found that most (16 of 19) of the identified studies related to populations with AS, with only three reporting on axSpA prevalence rates (which varied widely) and none reporting on nr-axSpA rates.[8]

2.1.4 Impact of health problem

Patients with nr-axSpA often have morning back stiffness, which improves with exercise but not with rest. They may also frequently awaken at night due to back pain, which improves if they get up and walk around. Functional impairment due to inflammation can have a major impact on health and quality of life, leading to withdrawal from active employment (resulting in adverse financial consequences). Reduction of pain and stiffness and the preservation of function and mobility, along with employment and participation in society, are the most important aims from a patient perspective.[9] Symptoms of nr-axSpA can vary over time, with worsening of symptoms during flare periods and other periods where symptoms are more manageable.

2.2 Current service provision

First line pharmacological treatment for nr-axSpA usually consists of non-steroidal anti-inflammatory drugs (NSAIDs). Patients who respond inadequately, or cannot tolerate, NSAIDs may then be offered a TNFα inhibitor (adalimumab, certolizumab pegol, etanercept, golimumab), also known as anti-TNFs. NICE guideline 65 recommends that treatment with adalimumab, certolizumab pegol, and etanercept should only be continued if there is clear evidence of response after 12 weeks, defined as:[10]

- a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value, or by 2 or more units, **and**
- a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

Although it is possible that earlier treatment may reduce the possibility of long-term structural damage, there is limited evidence on this. In TA497[11] - golimumab for treating non-radiographic axial spondyloarthritis - the committee considered TNFα inhibitors as a class, given the lack of difference between the clinical effectiveness results. Golimumab was approved as a treatment nr-axSpA using the same response criteria as described above. No registry data were available on the efficacy of a second or third TNFα inhibitor, although the clinical experts considered the efficacy is likely to reduce with each subsequent treatment. Sequential use of TNF inhibitors was not modelled because of lack of data.

2.3 Description of technology under assessment

Secukinumab (brand name Cosentyx) is a monoclonal antibody which neutralises the activity of IL-17A, a proinflammatory cytokine. Marketing authorisation for use in patients with nr-axSpA is expected to be granted in May 2020 (see Table 2 of the CS). The anticipated recommended method of administration is expected to make use of a 'loading' dose, being given subcutaneously at weeks 0,1,2,3 and 4 followed by monthly doses. Self-injection may be possible for some patients following training.

Figure 4 in the CS proposes the positioning of secukinumab in the treatment pathway. The ERG's clinical adviser anticipated that secukinumab would mostly be used either as a 2nd line biologic (in patients who did not respond at all to their first TNFα inhibitor) or as a last-line biologic (in patients who had some response to TNFα inhibitors).

[redacted]

2.4 Critique of company's definition of decision problem

The decision problem table presented in the company's submission (p14) is reproduced below in Table 1, together with the ERG's comments on how closely the submission matches the NICE scope. The population in the CS matches that in the NICE scope, although the ERG notes that the nr-axSpA population is intrinsically a clinically heterogeneous one.[12] This heterogeneity is exacerbated by methodological heterogeneity across trials (and across the NHS) regarding interpretation of 'objective signs of inflammation', particularly with respect to 'elevated CRP', see Section 3.3. The wording of the anticipated marketing authorisation (MA) for secukinumab is consistent with that of the comparator technologies, apart from the absence of the word 'severe' to describe nr-axSpA in the secukinumab MA. The ERG's clinical adviser was not aware of a well-recognised definition of 'severe' and understood it as being a somewhat vague description of the cumulative impact of pain, stiffness and disability.

Considering that two different dosing regimens were used in the secukinumab PREVENT trial, the ERG asked the company to clarify the dosage recommendation (p15 of the CS). The company stated that the loading dose was recommended by the EMA for the treatment of AS [redacted]. The rationale for this decision was not clarified by the company. The presence of the 'no load' trial arm was stated as being primarily to satisfy FDA criteria.

Previous NICE technology appraisals of TNFα inhibitors for nr-axSpA recommend adalimumab, certolizumab pegol and etanercept (TA383),[13] and golimumab (TA497)[11] within their marketing authorisations in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. The company's submission compares secukinumab 150mg once a month, both with or without loading doses in the first month, with the aforementioned recommended TNFα inhibitors at their licensed doses. Secukinumab does not act by binding to TNF but to interleukin-17A (IL-17A) and so offers a treatment option which has an alternative mechanism of action to the TNFα inhibitors.

Only trials of secukinumab and certolizumab pegol included patients who have had prior exposure to a biological therapy. The certolizumab pegol trials were selective in doing this by excluding primary non-responders (patients who did not achieve an initial response) and the secukinumab trial was selective in only allowing one prior TNFα inhibitor.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from NICE scope	ERG comment
Population	People with nr-axSpA with objective signs of inflammation, whose disease has responded inadequately to, or who are intolerant to, NSAIDs	As per scope	–	The clinical trial population broadly reflects the eligible population in England and Wales. However, heterogeneity exists across the trials and across the NHS regarding interpretation of 'objective signs of inflammation'.
Intervention	Secukinumab	As per scope	–	The intervention described in the CS matches the description in the final scope. The marketing authorisation is anticipated to recommend use of the loading dose of secukinumab.
Comparator(s)	• Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Established clinical management without biological treatments	As per scope	–	The comparators described in the company's submission match those described in the final scope.
Outcomes	The outcome measures to be considered include: • disease activity • functional capacity • disease progression • pain • peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • Symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis)	As per scope, except for peripheral arthritis, dactylitis, and symptoms of extra-articular manifestations.	These are not measured outcomes within the secukinumab Phase III study (PREVENT, NCT02696031).	Although some relevant outcomes were not evaluated in PREVENT, all appropriate outcomes were assessed with respect to generating suitable efficacy data for the economic model.

	• adverse effects of treatment • health-related quality of life			
Subgroups	If the evidence allows the subgroups of people who have, had or not had, prior exposure to biological therapy.	As per scope	–	Only trials of secukinumab and certolizumab pegol included a small proportion of patients who have had prior exposure to a biological therapy.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

The company submission included the searches to identify studies for 1) the systematic review of secukinumab in patients with nr-axSpA and 2) the network meta-analysis (NMA) of biological agents in the treatment of nr-axSpA. A detailed description of the searches was reported in Appendix D of the submission along with the search strategies used. The searches in general were appropriate to identify relevant trials. Limitations included: non-English language studies would not have been identified and any unpublished or ongoing studies may have been missed as the WHO ICTRP was not searched. The ERG's appraisal of the searches is summarised in Table 2.

Table 2 ERG appraisal of evidence identification

Issue	ERG response	Note
Is the report of the search clear and comprehensive?	Yes	Update search strategies were not included in the original submission although they were provided in the company response to the points for clarification.
Were appropriate sources searched?	Partly	No search of WHO International Clinical Trials Registry Platform (ICTRP).
Was the timespan of the searches appropriate?	Yes	Inception of databases to 16th September 2019. Conference abstracts 2016-2019 only.
Were appropriate parts of the PICOS included in the search strategies?	Yes	One extra comparator included which was not in the NICE scope – ixekizumab. Population was expanded to include ankylosing spondylitis as well as nr-axSpA.
Were appropriate search terms used?	Yes	
Were any search restrictions applied appropriate?	Partly	Retrieval restricted to English language articles. Reviews were removed from the searches of Embase and MEDLINE.
Were any search filters used validated and referenced?	Not applicable	Searches were not restricted by study design.

3.1.2 Inclusion criteria

The eligibility criteria used to select studies for inclusion in the systematic review of treatment effectiveness were presented in Table 8 of Appendix D of the CS. The ERG considers these criteria to be appropriate, with the exception of including studies of ixekizumab, which was not part of the NICE scope. However, no trials of ixekizumab were included in the network meta-analysis. No criteria were specified for the reporting of outcomes.

3.1.3 Critique of data extraction

The methods of data extraction were reported in the CS Appendix D. From the company's Excel spreadsheet of extracted data it was evident that the company had made use of data from documents relating to TA497 (the STA of golimumab).[11] However, no references were made to the data extracted and checked in the published HTA report of TA383 (which had nr-AxSpA trial data for adalimumab, etanercept, and certolizumab pegol).[14] Utilising these data would have minimised the risk of data extraction errors, such as the reported lack of BASDAI 50 data for the Haibel 2008 trial which did exist, and were reported in the HTA report of TA383 (see Table 8).

3.1.4 Quality assessment

The quality assessment of the studies identified for inclusion in the systematic review of effectiveness was reported in Appendix D of the CS. The methods used were appropriate for assessing trial internal validity, with sufficient detail to justify decisions provided in Appendix D. No assessment was made of trial external validity or applicability to the NHS setting.

3.1.4.1 Evidence synthesis

The evidence synthesis presented in the CS was a network meta-analysis. Details and further commentary on this analysis and the results are given in Section 3.4. The approach used was compatible with syntheses performed in a previous meta-analysis of TNFα inhibitors for both nr-axSpA and AS.[14]

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

The submission included one RCT of secukinumab, called PREVENT.[15]

3.2.1 Design and methods of the PREVENT trial

PREVENT is an international, multicentre, randomised, double blind, 3-armed parallel group study, which compares secukinumab given either with or without a loading dose with placebo. Design details and eligibility criteria were reported in sections B.2.3.1-B.2.3.7 of the CS. The key population eligibility criteria (Table 6 of the CS) appeared largely appropriate and relevant.

The trial appears to have robust internal validity (i.e. low risk of bias, see Appendix D, quality assessment section of the CS). However, no evaluation of PREVENT's external validity was presented. Of the 555 randomised patients, 24 were randomised in the UK. The ERG also notes the very large number of recruiting sites: 555 patients were recruited at 140 sites, averaging at around just 4 patients recruited per site. Concern has previously been raised about centres in multi-centre trials which recruit only a few patients. Their results may be less reliable since they may have less experience with the protocol than other centres; this could impact on patient selection, treatment administration, and evaluation of data and results.[16]

The ERG has some concerns that the patient selection issues[16] might have affected PREVENT. Firstly, the ERG notes the presence of a 'randomised set' for analysis which indicated that some patients may have been 'mis-randomised' by being 'mistakenly randomised … prior to the site confirming all eligibility criteria had been met' (p44, CS). Mis-randomised patients who did not receive any study medication were excluded from the data analysis sets (and treated as screening failures), so results for the true 'intention-to-treat' dataset were not reported. However, patients who *did* receive study medication were included. No data were presented in the CS to indicate how many ineligible patients were randomised and received treatment. However, the submitted interim clinical study report (CSR) reported that

[redacted]

Secondly, the ERG notes further possible problems with recruitment on p45 of the CS. The footnote states that, for the full analysis set, 'where patients were assigned to the wrong CRP/MRI stratification group at the study site, stratification group was overwritten by actual stratum'. No data were presented on how often this occurred. The ERG therefore has some concerns about the generalisability of the PREVENT population, due to the number of ineligible patients included, and the accuracy of the recording and stratification of CRP/MRI status across the numerous small study sites. In light of these issues the ERG is also concerned about the diagnostic eligibility criteria (CS, p35) which are: "Diagnosis of axSpA according to ASAS criteria". The ASAS criteria are not meant to be diagnostic, and it seems unclear whether enough attention was given to rule out other conditions, before arriving at a diagnosis of nr-axSpA.

The interim CSR also provided details on protocol deviations.

[redacted]

[redacted]

The PREVENT trial is ongoing, and the primary analysis time point for outcome assessments in the CS was at 16 weeks. Results for 52 weeks were also presented. The enrolment processes in PREVENT ensured that no less than 15% of patients were to belong to either of the three subgroups of "objective signs of inflammation": both elevated CRP and a positive MRI scan (CRP+ and MRI+), elevated CRP but a negative MRI (CRP+ and MRI-), and non-elevated CRP but positive MRI (CRP- and MRI+). MRI+ patients had evidence of sacroiliitis on an MRI scan and CRP+ patients had a baseline CRP level >5mg/l. Additionally, no more than 20% of patients could have had an inadequate response to a previous TNFα inhibitor therapy (termed "TNF-IR" patients).

Open label 'escape treatment' of 150mg secukinumab was available for all non-responders at 20 weeks. The ERG asked for further details on this. The company responded by stating that 'response' was based on "the clinical judgement of disease activity by the investigator and the patient to reflect the real-world setting". Therefore, no response criteria were pre-specified for the escape. The ERG has concerns about how relevant these criteria might be to the NHS setting which has implications for interpretation of the longer-term efficacy data. The company added that the original randomised treatment assignment (secukinumab 150 mg or placebo) remained blinded for at least 20 weeks.

The analysis of efficacy was based on the "full analysis set" which included all analysable patients who had been assigned study treatment (n=555). For the analysis of efficacy in the placebo-control phase of the trials, patients with missing binary data were imputed appropriately as non-responder outcomes. Appropriate methods were also used to impute missing continuous data – mixed-effects model repeated measures (MMRM).

3.2.2 PREVENT trial results

To get a more detailed picture of why patients were excluded from PREVENT, and why patients withdrew after being randomised, the ERG requested a detailed CONSORT flow diagram, reproduced here in [redacted]. This shows that to randomize and treat[redacted], reinforcing the ERG's aforementioned concerns about how patients were recruited. By way of contrast the two secukinumab trials in AS randomised 371 patients and excluded 77 at the screening

phase (MEASURE 1) and randomised 219 patients and excluded 34 at the screening phase (MEASURE 2).

[redacted]

The ERG's clinical adviser thought the baseline characteristics (Tables 9 and 10 of the CS) were reasonably representative of the patient population likely to receive a biologic in the NHS. However, the baseline BASFI scores (around 6) were noted to be higher than might be expected in practice; data from 12 registries in the EuroSpA collaboration indicate a median BASFI of around 5[17] and populations in the other clinical trials of TNFα inhibitors in nr-axSpA patients have mean BASFIs of around 5 to 5.5 (see Table 7).

The ERG's clinical adviser also thought it was unlikely that secukinumab would be used as a first line biologic therapy for most patients, so in clinical practice a higher proportion of patients will have received another biologic before commencing secukinumab. The ERG therefore considers it likely that the proportion of patients in PREVENT who have previously been treated with a biologic therapy (10%) may not be reflective of clinical practice in the NHS.

[redacted]

3.2.3 Main efficacy results for PREVENT

Clinical efficacy data for PREVENT were presented in section B.2.6 of the CS. Table 3 summarises the odds ratios or mean difference between arms for secukinumab "load" arm vs placebo in all patients for the main outcomes reported in the CS (adapted from Tables 16 to 32 of the CS). These results show that [redacted]. Results for the secukinumab "no load" arm compared to placebo were similar to the "load" arm, and so are not reproduced here (see Tables 16 to 32 of the CS). While results for the loading and no loading arms were very similar at 16 weeks there was some suggestion [redacted]

Table 3 Key outcomes results of the PREVENT trial: secukinumab "load" arm compared with placebo

Outcome	Odds ratio or mean difference	95% Confidence interval
ASAS 40	1.77	[redacted]
ASAS 5/6	[redacted]	[redacted]
BASDAI	[redacted]	[redacted]
BASDAI 50	[redacted]	[redacted]
BASFI	[redacted]	[redacted]
SF36 PCS	[redacted]	[redacted]
SF36 MCS	[redacted]	[redacted]
ASQoL	[redacted]	[redacted]
FACIT-fatigue	[redacted]	[redacted]
EQ-5D	[redacted]	[redacted]

SE Standard error, OR odds ratio, MD mean difference

All the outcomes reported in Table 3 were analysed using imputation for patients with no recorded response. For dichotomous outcomes patients with no record were assumed to be non-responders (non-responder imputation); for continuous outcomes a repeated measures model was used to impute responses from earlier time points. The ERG requested data on all outcomes without imputation in order to check the validity of the imputation process. The ERG performed a complete case analysis for all outcomes (i.e. an analysis where patients without recorded data at 16 weeks were excluded

entirely). The ERG found that these compete case analyses were either very similar to, or less conservative (i.e. bigger effect estimates) that the imputed results in Table 3. Therefore, the ERG considers the analyses with imputation to be valid and appropriate.

It is unclear how many patients would fulfil the NICE guideline 65 response criteria for continuation with treatment i.e. after 12/16 weeks it is unclear how many patients have:[10]

- a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units **and**
- a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more

The ERG identified data in a recent paper of a UK cohort of patients with axial spondyloarthritis (mostly patients with AS, but some with nr-AxSpA) which indicated that a BASDAI 50 response and/or a two or more points reduction was achieved by 409/508 (81%) patients, whereas a BASDAI 50 response was only achieved by 275 (54%). Response rates in AS are generally higher than for nr-axSpA, but these data imply that the proportion of patients who may continue on a biologic is higher in clinical practice than is indicated solely by BASDAI 50 trial results. This is also reflected in the high 'drug survival' rates reported by 12 European registries monitoring the use of biologics in axSpA; the EuroSpA collaboration reported that after 1 year 80% of patients were still taking their first biologic.[17] Considering the high placebo response rates for BASDAI 50 (21% in PREVENT) this has implications for the likelihood of even higher rates of placebo effects affecting continuation rates/ drug survival in the NHS, since it is easier to achieve a 2-point reduction in disease activity than it is a 50% reduction. There is also evidence to show that placebo effects can last much longer than a few weeks or months (see section 0).

3.2.3.1 [redacted]

3.2.3.2 Subgroup analyses

Objective signs of inflammation

The CS stated that pre-planned subgroup analyses were conducted according to randomisation strata of objective signs of inflammation (CRP+ and MRI+, CRP+ and MRI–, CRP– and MRI+) and previous biological treatment experience (naïve or inadequate response). The ERG requested more complete results details to those presented in the CS in Section B.2.7.2 and Appendix E. Results for key outcomes are reproduced in Table 4. A graph of ASAS 40 results for the TNF-naive population was also reported in the CSR, reproduced here as

*** [redacted] 2

Table 4 Selected subgroup results according to objective signs of inflammation, Week 16, FAS (adapted from Table 28 of the company's PfC response)

Stratification group	Treatment group	n/M (%) or n	LS mean change (SE)
ASAS40 response in all patients using non-responder imputation			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)		N/A
	Secukinumab 150 mg No Load (N=57)		
	Placebo (N=55)		
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)		
	Secukinumab 150 mg No Load (N=51)		
	Placebo (N=51)		
CRP– and MRI+	Secukinumab 150 mg Load (N=79)		
	Secukinumab 150 mg No Load (N=76)		
	Placebo (N=80)		
BASDAI change from baseline using MMRM			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)		
	Secukinumab 150 mg No Load (N=57)		
	Placebo (N=55)		
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)		
	Secukinumab 150 mg No Load (N=51)		
	Placebo (N=51)		
CRP– and MRI+	Secukinumab 150 mg Load (N=79)		
	Secukinumab 150 mg No Load (N=76)		
	Placebo (N=80)		

BASDAI50 response using non-responder imputation			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted]	N/A
	Secukinumab 150 mg No Load (N=57)	[redacted]	
	Placebo (N=55)	[redacted]	
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted]	
	Secukinumab 150 mg No Load (N=51)	[redacted]	
	Placebo (N=51)	[redacted]	
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted]	
	Secukinumab 150 mg No Load (N=76)	[redacted]	
	Placebo (N=80)	[redacted]	
BASFI change from baseline using MMRM			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=57)	[redacted]	[redacted]
	Placebo (N=55)	[redacted]	[redacted]
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=51)	[redacted]	[redacted]
	Placebo (N=51)	[redacted]	[redacted]
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=76)	[redacted]	[redacted]
	Placebo (N=80)	[redacted]	[redacted]
ASQoL change from baseline using MMRM			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=57)	[redacted]	[redacted]
	Placebo (N=55)	[redacted]	[redacted]
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=51)	[redacted]	[redacted]
	Placebo (N=51)	[redacted]	[redacted]
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted]	[redacted]
	Secukinumab 150 mg No Load (N=76)	[redacted]	[redacted]
	Placebo (N=80)	[redacted]	[redacted]
ASAS partial remission using non-responder imputation			
CRP+ and MRI+	Secukinumab 150 mg Load (N=54)	[redacted]	N/A
	Secukinumab 150 mg No Load (N=57)	[redacted]	
	Placebo (N=55)	[redacted]	
CRP+ and MRI–	Secukinumab 150 mg Load (N=52)	[redacted]	
	Secukinumab 150 mg No Load (N=51)	[redacted]	
	Placebo (N=51)	[redacted]	
CRP– and MRI+	Secukinumab 150 mg Load (N=79)	[redacted]	
	Secukinumab 150 mg No Load (N=76)	[redacted]	
	Placebo (N=80)	[redacted]	

[redacted] 2 [redacted]

[redacted]

Given these concerns about the effectiveness of secukinumab in patients who are MRI or CRP negative, the ERG asked the company - in a point of clarification (Q A.21) - to provide an indirect comparison of secukinumab with the available TNFα inhibitor evidence in the CRP+/MRI+, CRP+/MRI-, CRP-/MRI+ subgroups. The company identified only one trial (of etanercept, called EMBARK)[18] which had relevant, usable subgroup data[19] and used Bucher's method to compare secukinumab with etanercept with placebo as the common comparator. Although the MRI-/CRP+ subgroup was very small (n=15),

[redacted] The results of the company's Bucher comparisons are reproduced below in Table 5.

[redacted]

Table 5 Results of the Bucher indirect comparisons of secukinumab versus etanercept for MRI and CRP subgroups (reproduced from company's response to a point of clarification)

Outcome	Group	OR* (95% CI)
ASAS40	CRP -/MRI +	[redacted]
ASAS40 †	CRP +/MRI -	[redacted]
ASAS40	CRP +/MRI +	[redacted]
BASDAI50	CRP -/MRI +	[redacted]
BASDAI50 †	CRP +/MRI -	[redacted]
BASDAI50	CRP +/MRI +	[redacted]
ASAS40	Any CRP/MRI +	[redacted]
BASDAI50	Any CRP/MRI +	[redacted]
ASAS40 †	CRP +/Any MRI	[redacted]
BASDAI50 †	CRP +/Any MRI	[redacted]

†Correction factor of 0.5 applied as zero response is present in CRP+/MRI- subgroup in EMBARK study.

*Odds ratios >1 favour treatment with secukinumab

Experience of previous treatment with a biological therapy

Results for subgroups based on previous biological treatment were reported on pages 80-84 of the CS and also in Appendix E.

[redacted]

Placebo response rates

The ERG noted heterogeneity of placebo response rates across the trial subgroups (Table 6),

[redacted]

The ERG also notes that the size of the placebo response for BASDAI change from baseline in the TNF-naïve subgroup, a mean reduction

[redacted]

Table 6 Placebo response rates across subgroups at 16 weeks in the PREVENT trial

Population	Placebo response rate (%)	
	ASAS 40	BASDAI 50
Anti-TNF-naïve ([redacted])	[redacted]	[redacted]
TNF-experienced ([redacted])	[redacted]	[redacted]
MRI+/CRP+ ([redacted])	[redacted]	[redacted]
MRI+/CRP- ([redacted])	[redacted]	[redacted]
MRI-/CRP+ ([redacted])	[redacted]	[redacted]

3.2.3.3 Longer-term clinical effectiveness

Longer-term results were reported according to Analysis plan B (beginning on p73 of the CS), which analysed results for TNFα inhibitors naïve patients up to 52 weeks, using non-responder or MMRM imputation. The results have somewhat limited relevance to an NHS population due to the restriction to including only TNFα inhibitors naïve patients in the dataset and due to the continuation/stopping rules used. 'Inadequate response' was not formally defined but was instead decided following discussion between clinician and patient. In the NHS, BASDAI and VAS spinal pain criteria would be used (see section 2.2).

The ERG notes [redacted]. A similar rate at 52 weeks (16%) was seen for ASAS 40 in the most recent certolizumab trial,[20] although it is unclear why the placebo rates remain high for such a long period.

3.2.4 Adverse Events

Adverse events were reported on pages 107-121 of the CS. Safety data were presented for two time points in the PREVENT trial: the first 20 weeks of the trial, and the entire trial up to the data cut-off at 17 December 2018. Safety results were evaluated for four groups: secukinumab with loading, secukinumab with no loading, 'any secukinumab' (any patient who took secukinumab) and placebo. [redacted]

The number of patients in the placebo group started to decrease after week 20 when patients were allowed to switch to open-label secukinumab. The small number of patients in the placebo group, and the resulting lower number of patient-years exposure to placebo compared to secukinumab restricted the comparison between the two.

3.2.4.1 Safety data for up to Week 20

Adverse events (AEs) by system organ class (SOC) were summarised in Table 53 (p 109) of CS. The overall incidence of treatment-emergent adverse events (AEs) was [redacted] in the 'any secukinumab' group ([redacted]) than in the placebo group ([redacted]). The differences between the frequencies per SOC were small [redacted]. Overall, the most commonly reported AEs for 'any secukinumab' were [redacted] The incidence rates for serious adverse events (SAEs) were [redacted] for all four treatment groups (Table 55, p111 of the CS).

3.2.4.2 Safety data for the entire treatment period (up to 17th December 2018)

AEs for the entire treatment period were given in Tables 56, 57 and 58 (pp 112-114 of the CS). [redacted]

3.3 The company also presented exposure-adjusted incidence rates (EAIRs) in Tables 59 and 60 (p 116)

[redacted] ***The exposure to study treatment was reported in Table 52 (p 108 of the CS).*** [redacted] ***Critique of trials identified and included in the NMA***

The methods used in the company's systematic review (reported in Appendix D of the CS) were largely appropriate and have been discussed in Section 3.1. The ERG did not undertake independent searches to check that all relevant studies were included in the NMA, owing to time constraints. PRISMA flow diagrams are presented in Appendix D of the CS, along with tables of the included and excluded studies and the quality assessment results. The included RCTs were judged to generally be at a low risk of bias, which the ERG concurs with.

The systematic review identified 9 eligible RCTs, with the base-case NMA including data from 7 RCTs. The studies excluded from the NMA were:

- ABILITY-3, which compared efficacy in patients randomised to adalimumab treatment withdrawal (placebo) versus continuation in patients who had achieved sustained remission. This trial was therefore different to the other trials included in the NMA as it was conducted in a population who had already achieved a sustained response to adalimumab
- ESTHER, trial of etanercept vs sulfasalazine, which was excluded from the network for not having a placebo control group. The ERG also notes that around half the included patients had AS, since they fulfilled the New York criteria. The ERG would have excluded this study as results for the nr-axSpA subgroup were not reported.

[redacted]

Other sources of heterogeneity across trials were evident from Table 7. On p85 the CS stated that their "*evidence base was restricted to anti-TNF naïve patients who showed objective signs of inflammation to align with the final scope*". However, Table 7 shows that the EMBARK trial of etanercept included some patients who did not have objective signs of inflammation (i.e. MRI-/CRP- patients). Results excluding these patients are only available for the ASAS 40 outcome (and the company did not use

this result in their analyses). The CS did not highlight that the EMBARK results included a subgroup of patients without objective signs of inflammation and that the EMBARK results may therefore be conservative, when compared with the other trials. Similarly, for the two trials of certolizumab, a small proportion of patients who had previously received a TNFα inhibitor "anti-TNF-IR patients" were included in the cohort (i.e. not all patients were naïve to TNFs) so this is likely to slightly underestimate the efficacy of certolizumab relative to the TNF-naïve trial cohorts.

'Elevated CRP' - one of the 'objective signs of inflammation' is not defined in the biologic marketing authorisations. Across the trials there was wide variation in the cut-offs used to define elevated CRP, ranging from 3mg/l to 10mg/l (Table 7); the trial mean CRPs reflected this variation in cut-offs. Moreover, the secukinumab CRP data show that the mean values are less representative of the population than the medians, since some patients may have very high CRPs which can make the means much larger than medians. Most trials reported only mean CRPs, although the RAPID-AxSpA trial reported high medians – more than twice those reported in PREVENT.

[redacted]

Table 7 Clinical and methodological trial characteristics which might affect response rates

	PREVENT[15]	RAPID AxSpA [21]	C-AxSpAnd [20]	GO-AHEAD [22]	EMBARK [18]	ABILITY-1 [23]	Haibel 2008 [24]
Biologic therapy	SEC	CZP	CZP	GOL	ETA	ADA	ADA
No. of patients randomised	185 SEC L, 184 SEC NL, 186 PLA	51 CZP Q4W, 46 CZP Q2W, 50 PLA	159 CZP, 159 PLA	98 GOL, 100 PLA	106 ETA, 109 PLA±	91 ADA, 94 PLA±	22 ADA, 24 PLA
Trial Methodology							
Recruitment period	2016-2019	2010-2011	2015-2018	2012-2014	2011-2012	2009-2011	2005-2007
No. of study sites	140	83	80	52	NR 14 countries	37	2
Randomisation ratio	1:1:1	1:1:1	1:1	1:1	1:1	1:1	1:1
No. of trial arms	3 (2 active)	3 (2 active)	2	2	2	2	2
Dose/Frequency of injections	150mg weekly to week 4, then monthly	200mg Q2W or 400mg Q4W	400mg at wks 0, 2, 4, then 200mg Q2W	50mg every 4 weeks	50mg per week	40mg every other week	40mg every other week
Primary efficacy timepoint	16 weeks	12 weeks	12 & 52 weeks	16 weeks	12 weeks	12 weeks	12 weeks
Imputation - missing continuous data	[redacted]	LOCF	LOCF	LOCF	LOCF	LOCF	N/A
% with missing	[redacted]	NR at 12	7 at 52 wks	4	4	3	0

	PREVENT[15]	RAPID AxSpA [21]	C-AxSpAnd [20]	GO-AHEAD [22]	EMBARK [18]	ABILITY-1 [23]	Haibel 2008 [24]
Biologic therapy	SEC	CZP	CZP	GOL	ETA	ADA	ADA
continuous data		wks ~ 7% at 24 wks					
Key baseline characteristics							
BASDAI (mean)	7.1 SEC L, 6.9 SEC NL, 6.8 PLA	6.5 Q2W, 6.6 Q4W, 6.4 PLA	6.9 Q2W, 6.8 PLA	6.6 GOL, 6.4 PLA	6.0 ETA, 6.0 PLA	6.4 ADA, 6.4 PLA	6.5 ADA, 6.2 PLA
BASFI (mean)	6.2 SEC L, 5.9 SEC NL, 5.9 PLA	4.8 Q2W, 5.1 Q4W, 4.9 PLA	5.4 Q2W, 5.4 PLA	5.3 GOL, 4.8 PLA	4.2 ETA, 3.9 PLA	4.5 ADA, 4.8 PLA	5.4 ADA, 4.9 PLA
Mean symptom duration, years (mean)	[redacted]	4.8 Q2W+, 7.3 Q4W+, 4.5 PLA+	7.8 Q2W, 8.0 PLA	NR but < 5 years	2.4 ETA, 2.5 PLA	10.7 ADA, 10.5 PLA*	7 ADA, 8 PLA
CRP level mg/l (mean, medians are +)	[redacted]	10 Q2W+, 12.1 Q4W+, 13.5 PLA+	15.8 (both arms)	15 GOL, 13PLA	6.8 ETA, 6.4 PLA	ADA 8.6, 9.3 PLA*	6.2 ADA, 7.8 PLA
Definition of CRP+	[redacted]	>7.9 mg/l	ULN=10 mg/l	"ULN"	>3mg/l CRP	'elevated'	>6mg/l
% CRP+	[redacted]	63	56 CZP, 53 PLA	41 (both)	45 ETA, 40 PLA	32 ADA, 39 PLA	38
% MRI+	[redacted]	54	NR	67 GOL, 66 PLA	82 ETA, 80 PLA	51 ADA, 47 PLA	55 ADA, 75 PLA
% MRI+ and CRP+	[redacted]	NR	29 CZP, 27 PLA	NR	NR	20 ADA, 16 PLA	NR

	PREVENT[15]	RAPID AxSpA [21]	C-AxSpAnd [20]	GO-AHEAD [22]	EMBARK [18]	ABILITY-1 [23]	Haibel 2008 [24]
Biologic therapy	SEC	CZP	CZP	GOL	ETA	ADA	ADA
% MRI- and CRP-		0	0	20 (for both)	11 ETA, 13 PLA	37 ADA, 31 PLA	NR
% MRI+ CRP-		NR	47 CZP, 48 PLA	NR	NR	31 ADA, 31 PLA	NR
% MRI- and CRP+		NR	24 CZP, 25 PLA	NR	NR	12 ADA, 22 PLA	NR
% Concomitant NSAID		84	87	NR	~100**	79	NR
% Concomitant DMARD		25	32	NR	20	18	0
% Anti-TNF naïve		89[x]	94[x]	100	100	100	98
Response rates							
% ASAS 40 placebo rate		16	11	23*	17*	14*	13
% BASDAI 50 placebo response rate		16	NE	29*	24	14*	21
% ASAS 40 active drug response rate		48 Q2W, 47 Q4W	48	60*	35*	41*	55
% BASDAI 50 active drug response rate		50 Q2W, 47 Q4W	NE	59*	44	39*	50

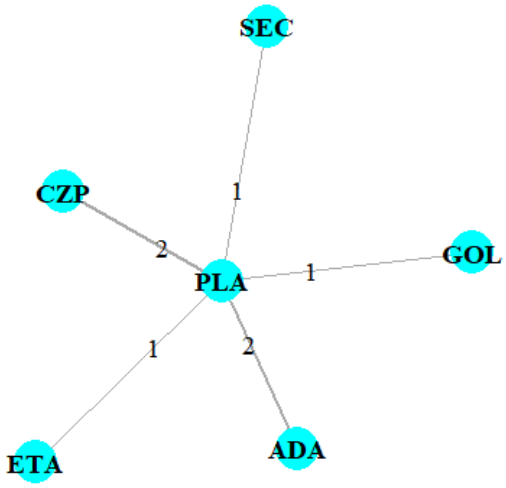
ADA Adalimumab, CZP Certolizumab, ETA Etanercept, GOL Golimumab, TNF-IR Tumour necrosis factor-inadequate response, L Load, LOCF Last observation carried forward, MMRM Mixed-effects model repeated measures, MTX methotrexate, N/A Not applicable, NE Not evaluated, NL No load, Q2W every 2 weeks, Q4W every 4

weeks, SEC Secukinumab, SFZ Sulfasalazine ULN Upper limit of normal, wks weeks. [±] Includes some unlicensed patients i.e. those without objective signs of inflammation: licensed population for ABILITY-1 was n=69 ADA, 73 PLA and for EMBARK n=94 ETA, 95 PLA, [*] for licensed population (MRI+ and/or CRP+), [**]NSAID dose and type were to remain stable - patients who could not continue NSAIDs were withdrawn, [+] Medians, [x]TNF 'primary failure' patients excluded (i.e. those with no response within the first 12 weeks)

3.4 Critique of the indirect comparison

The company conducted an NMA to compare the relative efficacy of secukinumab compared to TNFα inhibitors that have been approved for the treatment of nr-axSpA. The comparator treatments were etanercept, adalimumab, golimumab, and certolizumab pegol. None of the active treatments were compared to each other directly in trials, and therefore the common placebo comparator was used to form a (star shaped) network connecting all the treatments. The overall network diagram is reproduced in Figure 3. The outcomes that were considered most important for synthesis were: (i) ASAS 40, (ii) BASDAI 50, (iii) BASDAI change from baseline (CFB), and (iv) BASFI CFB; as they would be used in the economic model. Data were combined across 12-16 weeks to utilise all available evidence. The secukinumab data obtained at 16 weeks were used as base-case, but data at 12 weeks were used for sensitivity analysis.

Figure 3 Diagram for the overall network



The numbers on the lines represent the number of trials comparing the two connected treatments. ADA= adalimumab, CZP= certolizumab pegol, ETA= etanercept, GOL=golimumab, PLA= placebo and SEC= secukinumab.

The NMA models used were detailed in Appendix D of the CS (pp 50-57) and in the NMA report provided by the Company in their PFC response.[25]

A variety of NMA models were fitted, modelling outcomes independently and jointly, and making different assumptions about the data. Independent outcomes were modelled using recommendations from the NICE DSU detailed in TSD 2[26] and the report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices.[27] Categorical responses (ASAS 40 and BASDAI 50) were analysed using a generalised linear model with a logit link function and binomial likelihood,

whereas continuous responses (changes in baseline for BASDAI and BASFI) were modelled using identity link functions and normal likelihoods. Fixed and random effects models were fit assuming identical, independent, and exchangeable treatment effects.

The base case NMA incorporated in the economic modelling was based on the joint modelling approach used in TA383.[14] In this model, responses on BASDAI 50 and BASDAI change from baseline were related to each other and BASDAI and BASFI change from baselines were assumed to be correlated. All TNFα inhibitors were assumed to have an exchangeable treatment effect, i.e. the treatment effects are similar but not identical. Inferences about the effectiveness of each TNFα inhibitor borrow strength across the treatment class, shrinking the estimates towards the mean of the class effect. The CS uses these shrunken estimates in their economic model. Only fixed effects models were fitted, i.e. between-study heterogeneity was not considered in the joint modelling.

The company only conducted sensitivity analyses on the independent (uncorrelated) outcome models (summarised in Table 43 (p88) of the CS). In addition to using the 12-week data, the sensitivity analysis examined (i) placebo response-adjusted models (to explore the heterogeneity in placebo response between studies), (ii) the use of informative priors on random effects and (iii) the exclusion of studies that could potentially be outdated.[24]

Meta-regression was used to explore the heterogeneity of baseline characteristics, but there was insufficient evidence to make any conclusions. Details on meta-regression as supplied in Appendix D.1.3.2 of the CS and the NMA report.[25]

The ERG considers that the NMA approach used in the CS is valid and appropriate, but notes that, because there are few trials and no-head-to-head comparisons of treatments, there is no potential for checking for consistency in the network, even though this is a fundamental assumption. In addition, there are too few trials to estimate between-study heterogeneity and a fixed effect model was used. If, however, there are meaningful differences on patient characteristics or trial conduct across the included trials, these assumptions may lead to bias and/or inflated precision.

3.4.1 Data

The ERG found discrepancies in the data used in the company's NMA models and considered some of the methods used to prepare the data for analysis to be inappropriate. The ERG referred to the analysis on nr-axSpA in TA 383[13, 14] which included 4 of the 7 studies in the NMA to check the data.

The company did not always extract the correct data. In the case of Haibel[24], the response on BASDAI 50 outcome was missed entirely. For EMBARK,[18] N in the treatment arm was not correct. For the GO-AHEAD trial data were extracted from TA497.[11] However, baseline BASDAI and the

corresponding standard deviation (SD) appear to be extracted from Sieper *et al*[28] where the number of patients in both arms are inconsistent from the former source.

In Section 4.6 of their NMA report[25], the company explains the methodology used to calculate SDs for CFB scores when they are unavailable. This method was used for two studies: Haibel[24] and C-axSpAnd.[20]. However, in their calculations the company assumed that there was no correlation between the baseline and follow-up values (although they state that a sensitivity analysis with a correlation of 0.5 was carried out too). The ERG prefer to include an assumed correlation as recommended by the Cochrane Handbook[29] and used in TA383.[14] A correlation of 0.3 was chosen, as used in TA383.[14]

In RAPID-axSpA,[21] two certolizumab pegol treatment arms of different doses were pooled into a single treatment arm for the purpose of the NMA. In the NMA report, the company stated that they used a weighted average of the two arms. However, it was unclear how they calculated the SEs corresponding to the CFB scores. The ERG re-calculated the standard errors(SEs) using methods suggested by the Cochrane Handbook[29] and used in TA383.[14].

The ERG repeated the NMA for the base-case model used in the economic modelling using a revised data set (given in Table 8) that corrected these mistakes.

Table 8 Data used in NMA models by the ERG. The values in the shaded cells differ from those used by the company in their submission

Study	Treatment	N	BASDAI 50	Baseline BASDAI		BASDAI CFB		BASFI CFB	
			Response	Mean	SD	Mean	SE	Mean	SE
ABILITY	PLA	73	10	6.38	1.51	-1.10	0.23	-0.63	0.21
	ADA	69	27	6.43	1.54	-2.20	0.30	-1.28	0.24
RAPIDAXSPA	PLA	50	8	6.50	1.50	-1.50	0.40	-0.40	0.40
	CZP	97	47	6.55	1.51	-3.35	0.29	-2.3	0.29
EMBARK	PLA	109	26	6.00	1.90	-1.30	0.30	-0.80	0.20
	ETA	106	46	6.00	1.80	-2.00	0.30	-1.40	0.20
GOAHEAD	PLA	80	23	6.40	1.50	-1.51	0.28	-0.87	0.25
	GOL	78	46	6.60	1.60	-3.69	0.28	-2.78	0.25
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HAIBEL	PLA	24	5	6.20	1.30	-1.20	0.48	-0.80	0.56

	ADA	22	11	6.50	1.20	-2.70	0.52	-2.40	0.53
CAXSPAND	PLA	158	NA	6.79	1.28	-1.08	0.17	-0.50	0.22
	CZP	159	NA	6.88	1.40	-2.95	0.18	-2.19	0.21

SD= Standard deviation, SE=Standard error, CFB= Change from baseline. ADA= Adalimumab, CZP= Certolizumab pegol, ETA= Etanercept, GOL=Golimumab, anti-TNF=TNFα inhibitors and SEC= Secukinumab.

3.4.2 NMA Models and Results

The company presents the results of the NMA models in pages 90-104 of the CS. Further details are provided in Appendix D and the company's NMA report.[25]

[redacted] Correlated or joint models were preferred by the company, as the relationships between the outcomes should not be ignored when synthesising evidence. The company followed the preferred modelling approach in TA383,[14] which is also the ERG's preference.

The change from baseline in BASDAI and BASFI scores are correlated and BASDAI 50 is the probability of a 50% reduction in the BASDAI score. In order to model these relationships in a joint model, changes in BASDAI scores were assumed to be correlated to changes in BASFI scores, with correlations estimated by the model. In order to relate the BASDAI 50 score to the change in BASDAI score, the BASDAI score at baseline was assumed to be correlated to the change score using a bivariate normal distribution. The bivariate normal distribution was defined using:

(i) mean BASDAI score at baseline
(ii) standard deviation (SD) for the mean BASDAI score at baseline
(iii) change in BASDAI score in placebo

[redacted].

[redacted]

The ERG did not find it appropriate to pool across all trials as the patient populations differed in terms of prior biologic use. Of the other studies in the NMA, C-axSpAnd[20] and RAPID[21] had a population of biologic-naïve patients comparable to PREVENT.

For alternative baseline values, the ERG looked at the EuroSpA study[17 119] that combined 12 European registries and reported the characteristics of 1,178 individuals with nr-axSpA who were biologic-naïve to estimate the baseline BASDAI and the corresponding SD. To estimate the BASDAI CFB score, the ERG used the weighted average of the BASDAI CFB score for the placebo arms of relevant trials (i.e. PREVENT, C-axSpAnd and RAPID).

The ERG also conducted an analysis exclusively using baseline parameters reported in PREVENT. However, the ERG considered the baseline values reported in the EuroSpA to be a better representation of the treatment population compared to those reported in PREVENT considering the concerns discussed in Section 3.2.2.

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* 95% Credible Intervals

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		95% CrI	[redacted]	[redacted]	[redacted]
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		Median		[redacted]	[redacted]
		95% CrI	[redacted]	[redacted]	[redacted]
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		Median		[redacted]	[redacted]
		95% CrI	[redacted]	[redacted]	[redacted]
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		Median		[redacted]	[redacted]
		95% CrI	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Mean	[redacted]	[redacted]	[redacted]
		Median		[redacted]	[redacted]
		95% CrI	[redacted]	[redacted]	[redacted]
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		Median		[redacted]	[redacted]
		95% CrI	[redacted]	[redacted]	[redacted]
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		Median		[redacted]	[redacted]
		95% CrI	[redacted]	[redacted]	[redacted]
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		95% CrI	[redacted]	[redacted]	[redacted]
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		95% CrI	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Mean	[redacted]	[redacted]	[redacted]
		Median		[redacted]	[redacted]
		95% CrI	[redacted]	[redacted]	[redacted]

* SD of mean class effect

** The ERG was able to reproduce this set of results

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3.4.2.1 Sensitivity Analysis

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3.4.2.2 [redacted]

3.4.2.3 Pooling Load and No Load Data

The ERG considered whether using evidence only from the loading arm of PREVENT is appropriate to establish the effectiveness of secukinumab. The PREVENT trial shows no statistically significant or clinically meaningful difference between the two arms in the range of outcomes evaluated at 16-weeks – see Table 12. For this reason, the ERG considers that the 16-week results from the load and no-load arms of PREVENT could be reasonably pooled to inform the effectiveness of secukinumab at 16 weeks and beyond (either regimen). Given the similarity in outcomes across the two arms, combining the information will not affect expected results, but it can significantly reduce the existing uncertainty surrounding the treatment effect of secukinumab in relation to TNFα inhibitors. In the response to clarification, the company argued that PREVENT showed a *"consistent trend towards numerically higher efficacy responses*" in the load arm. [redacted]

[redacted] Given the equivalence in clinical outcomes between arms at 16 weeks, the ERG's clinical advisor did not expect any further differences between the arms beyond that.

Table 12 ASAS 40, BASDAI 50, change from baseline BASDAI and change from baseline BASFI for load and no-load arms of secukinumab. 16-weeks results from PREVENT trial

Outcome	Load secukinumab	No load secukinumab
ASAS 40, n/N(%)	[redacted]	[redacted]
BASDAI 50, n/N(%)	[redacted]	[redacted]
BASDAI change from baseline, mean (SD)	[redacted]	[redacted]
BASFI change from baseline, mean (SD)	[redacted]	[redacted]

[redacted]

3.5 Conclusions of the clinical effectiveness section

The clinical evidence for secukinumab is currently based a single, ongoing, placebo-controlled RCT, the PREVENT trial. This trial was appropriately conducted, reporting suitable clinical outcomes and with a sufficiently large sample size (555 patients) to have sufficient power to demonstrate the effectiveness of secukinumab. However, the ERG has some concerns about population generalisability, given the significant number of ineligible patients randomised across the numerous small study sites.

The PREVENT trial showed substantial clinical benefits of secukinumab when compared to placebo across all reported outcomes, with analyses being statistically significant with large treatment effects that are likely to be of clinical importance. Secukinumab can therefore be reasonably assumed to be an effective treatment for reducing nr-axSpA symptoms. Secukinumab appears to have an acceptable safety profile.

The PREVENT trial included [redacted] who had previous exposure to a TNFα inhibitor. Although relative effect estimates versus placebo were similar across the two subgroups (TNF-naïve and TNF-experienced), the TNF-experienced subgroup was too small to provide any

conclusive evidence about similarity of efficacy. For the TNF-experienced subgroup, comparisons with placebo were not statistically significant for several key outcomes and confidence intervals were wide.

The PREVENT trial also considered other subgroups of patients: those with evidence of inflammation from both MRI imaging and elevated CRP levels (MRI+/CRP+) compared to those with only one of the two (MRI-/CRP+ and MRI+/CRP-). [redacted] According to clinical advice given to the ERG, most patients in the UK diagnosed with nr-axSpA will have a positive MRI scan, but it is somewhat unclear how many patients might be considered for secukinumab in the MRI-/CRP+ group.

[redacted]

Given the lack of head-to-head evidence it is important to consider the plausibility of such an effect. On the one hand, secukinumab showed similar efficacy to TNF-alpha inhibitors in AS (TA407 FAD 4.10). The clinical advisor highlighted that AS and nr-axSpA are perceived as parts of a spectrum of axSpA conditions. Hence, evidence of effect in AS may have some relevance to an nr-axSpA population. However, the PREVENT trial in nr-AxSpA showed consistently lower effectiveness for

secukinumab when compared to placebo across several outcomes. The ERG therefore considers that, based on the current limited evidence, the NMA results should be considered at face-value. Data on the MRI/CRP subgroups were sparse, being reported in only two trials.

Overall, secukinumab appears to be an effective treatment for nr-axSpA, but is unlikely to be clinically preferable to existing TNFα inhibitors for most patients. It may therefore be best considered as a treatment for use where TNFα inhibitors are unsuitable or unavailable. Although evidence is too limited to draw firm conclusions, secukinumab may also be of value for patients where TNFα inhibitors have proved ineffective.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The ERG is satisfied with the company's review of the cost-effectiveness literature. Briefly, the company did not find any studies that evaluated the use of secukinumab in nr-AxSpA. However, seven economic evaluations that assessed other drugs for nr-AxSpA and were relevant to the UK population, met the inclusion criteria. Two were published studies,[14, 32] three were company submissions to NICE for TA383 (by Abbie, Pfizer, and UCB),[13] and two were submissions to the Scottish Medicines Consortium (SMC).[33, 34] Amongst these, four economic evaluations used a decision tree for short-term response followed by a Markov model to capture long-term costs and effects. The three remaining studies used a decision tree, a state-transition model and a patient-level simulation model. The characteristics of the identified studies are summarised in Table 7 of Appendix G of the CS.

Points for critique

In general, the searches were likely to have identified relevant cost-effectiveness studies, however only those published in English. The use of a validated search filter for identifying economic evaluations, or adding further subject heading and free-text terms relating to economic evaluations to the strategies for MEDLINE and EMBASE may have ensured a more comprehensive search.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

The company submitted a Markov model that tracks nr-axSpA patients through lifetime. Patients initially receive either secukinumab, TNFα inhibitors, conventional care for an induction period of 12 weeks (for TNFα-inhibitors) or 16 weeks (for secukinumab) after which response is assessed determining continuation of the biologic or, in case of non-response, discontinuation to conventional care. The company submits a number of analyses using this model:

In the base-case analysis, the company compares secukinumab 150mg with loading, different TNFα inhibitors and conventional care for 1st line treatment of TNF-naïve patients with inadequate response or intolerance to ≥2 NSAIDS. This analysis is largely based on results observed for the TNF-naïve subgroup of the PREVENT trial and in the NMA where all outcomes are considered simultaneously and a class effect for TNFs is implemented (but TNF specific estimates are used).

In a scenario, secukinumab was compared only against conventional care for 2nd line use; that is after one TNFα-inhibitor has failed to produce adequate response or was discontinued due to adverse events. This analysis is largely based on results observed for the TNF-experienced subgroup of the PREVENT trial.

In response to the ERG's clarification questions, the company submitted further scenario analyses. These analyses will be described in the critique section below (sections 4.2.1 - 4.2.11), where the rationale for requesting these is also presented.

History of NICE appraisals

NICE has previously appraised the use of biologics in AS and nr-axSpA in three separate instances:

- TA383 (MTA, replacing TA143)[13] considered the use of TNFα inhibitors in severe AS and nr-axSpA. For severe nr-axSpA, TA383 recommends adalimumab, certolizumab pegol and etanercept in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs.
- TA407 (STA)[35] recommends secukinumab (under a patient access scheme) as an option for treating active AS in adults whose disease has responded inadequately to conventional therapy (non-steroidal anti-inflammatory drugs or TNF‑alpha inhibitors).
- TA497 (fast-track appraisal)[11] recommends golimumab as an option for treating severe nr-axSpA in adults whose disease has responded inadequately to, or who cannot tolerate, nonsteroidal anti-inflammatory drugs.

The committees, in their decision-making process, made a number of important considerations. The ERG will refer to these when reviewing the relevant sections.

4.2.1 NICE reference case checklist

The concordance between the model included in the CS and the NICE reference case is detailed in Table 13.

Table 13 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate
Perspective on costs	NHS and PSS	The CS is appropriate
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate. Patients enter at the age of 39 years old and a maximum age of 100 is assumed
Synthesis of evidence on health effects	Based on systematic review	Evidence synthesis is based on the 'Load' arm of the PREVENT trial and the 'No-Load' arm evidence is disregarded. Given that effectiveness is almost identical between the 'Load' and

		the 'No-Load' arms of PREVENT trial, combining both arms has the potential to greatly reduce uncertainty surrounding the relative effectiveness of secukinumab in comparison to TNFα-inhibitors
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The CS is appropriate. HRQoL is measured in QALYs. EQ-5D-5L collected directly from the PREVENT trial is used
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Population

The company's submission considers patients with nr-axSpA as defined by the 2009 ASAS classification criteria[36] with objective signs of inflammation (sarcoiliitis on MRI and/or elevated CRP levels, hereby identified as MRI+ and/or CRP+), who were intolerant or whose disease has responded inadequately to treatment with ≥ 2 NSAIDS. The submission considers two patient groups separately: biologic-naïve and biologic-experienced patients (i.e. patients who have received only one previous TNFα-inhibitor, as per recruitment into PREVENT). The PREVENT trial was used to define the characteristics of the populations in the model (Table 14). Note that for both populations the company used the same baseline BASDAI and BASFI, and the ERG believes the values used reflect the biologic-naïve patients in PREVENT.

Table 14 Baseline patient characteristics for biologic-naïve and biologic-experienced subgroups in the economic model.

	Assumed in the model	
Parameter	**Biologic-naïve (N=501)**	**Biologic-experienced (N=54)**
Mean age (years)	39.0	42.8
Male (%)	46.1%	44.4%
Baseline BASDAI	[redacted]	
Baseline BASFI	[redacted]	

Points for critique

As referred to in Section 3.2.2, 3.3 and 3.4.2, the sample enrolled in the PREVENT trial shows a higher BASFI value than the samples in other nr-axSpA trials and in the recent EuroSpA registry[17]. The ERG therefore considers:

item 1. BASFI baseline values in EuroSpA are likely to better reflect 1st line nr-axSpA patients

The ERG considered the relevance of the scenario analyses considering biologic experienced patients. The ERG notes that the different populations analysed (biologic naïve and experienced) reflect different options for the positioning of secukinumab in the treatment pathway. In particular, the base-case analysis, which includes TNF-naïve patients, considers secukinumab as 1st line treatment and the biologic experienced subgroup as 2nd line treatment (after one previous TNFα-inhibitor has failed). The company's analyses of biologic-experienced patients, however, is based on a very small subgroup of PREVENT: only [redacted] of the [redacted] patients recruited were biologic-experienced with only [redacted] being randomised to secukinumab with loading and [redacted] to placebo. For this reason, the ERG considers that PREVENT does not provide adequate evidence of the 2nd line use of secukinumab. Despite the absence of relevant evidence, and as highlighted ahead (Section 4.2.11), the ERG considers the 2nd line positioning of secukinumab as a relevant option in clinical practice, alongside its use at end-of-line (that is, after failure of 2 or 3 TNFα-inhibitors). The ERG identified that:

item 2. PREVENT does not provide adequate evidence of the 2nd line use of secukinumab.

4.2.3 Interventions and comparators

The intervention in the cost-effectiveness model is 150mg of secukinumab with loading dose, i.e. secukinumab is administered at weeks 0,1,2,3,4 followed by one dose every four weeks. Comparators in the company's analysis of the TNF-naïve population include conventional care (NSAIDS and physiotherapy) and individual TNFα inhibitors currently licenced for nr-axSpA, namely adalimumab,

certolizumab pegol, etanercept and golimumab. Biosimilars for adalimumab and etanercept are used and assumed clinically equal to the original patented product. The licenced dosage of each agent along with its frequency of administration are found in Table 64 of the CS. The intervention and the TNFα inhibitors are subject to a response-based stopping rule to be assessed after a fixed induction period. For TNFα-inhibitors, NICE guidance recommends that response to TNFα inhibitors and secukinumab is based on a reduction of the BASDAI to 50% of the baseline value or a reduction of 2 units or more, together with a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.[10] If an adequate response is not achieved 12 weeks after treatment initiation, treatment should be stopped (TA 383 FAD 4.69). Note that the proposed induction period for secukinumab is 16 week and differs from the TNFα inhibitors induction period which is 12 weeks. In the appraisal of secukinumab for AS (TA 407), the Committee concluded that the 16-week assessment of response was in line with the marketing authorisation and was hence acceptable for decision making (TA 407 FAD 4.7).

In the biologic experienced population, secukinumab was not compared with TNFα-inhibitors, but only with conventional care.

Points for critique

The ERG considered which of the secukinumab dosing regimens (with or without loading in the first month) should be considered. The submission shows no evidence of a difference in clinical outcomes between the load and no-load regimes across all primary and secondary outcomes (evaluated at 16 weeks) and subgroup analyses (Tables 36, 38, 39, 40, 41 of the CS). The regimen with no loading does not include administration at Weeks 1,2,3, which results in [redacted] less cost per patient. The regimen of secukinumab without loading is less costly than the regimen with loading, with no evidence that it is less effective at 16 weeks and beyond. Hence, the ERG believes:

item 3. unless the MA specifies otherwise, the regimen of secukinumab with no loading should be considered as the relevant intervention.

The ERG considered whether each individual TNFα-inhibitor should be used as a different comparator. In TA383 the committee concluded that, given the lack of difference in the effect of TNFα inhibitors (supported by the more complete evidence set in AS), they should be considered as a class with broadly similar, if not identical, effects.[13] Since TA383, two new trials on TNFα inhibitors (certolizumab pegol and adalimumab) have been published, but their inclusion in the NMA did not alter conclusions (Section 3.5). The ERG therefore believes, in line with the considerations made in TA383:

item 4. a single comparator representing the class of TNFα inhibitors should be considered.

In response to the ERG's clarification question B2, the company updated their economic model to include a single TNFα-inhibitor comparator, using the predictive distribution of the class-effect implemented in the NMA representing the effectiveness of the class.

In evaluating the cost-effectiveness of 1st line use of secukinumab the company's model does not consider subsequent treatment with biologics. Given that patients are eligible (and likely) to receive such further treatments, it is important that the outcomes and costs of further lines of therapy are considered when establishing the cost-effectiveness of 1st line use of secukinumab. The ERG therefore considers that:

item 5. subsequent treatment with biologics should be incorporated in the model to establish the cost-effectiveness of 1st line use of secukinumab.

The ERG also considered whether conventional care is the only comparator when secukinumab is positioned in second line of therapy. NICE recommends sequential use of TNFs (TA383 FAD 4.70) and hence these are relevant comparators to secukinumab in 2nd line. The company disputes this by citing the Regional Medicines Optimisation Committee (RMOC) Advisory Statement[37] on the use of biologics across conditions which recommends switching mechanism of action when a biologic treatment fails. However, the RMOC also highlights that if treatment failure can be attributed to the development of anti-drug antibodies a 2nd line treatment of the same class may be preferable in order to avoid treatment interruption. The ERG's clinical advisor confirmed that this is a known mechanism for loss of response to anti-TNFs in nr-axSpA patients. Hence, the ERG considers that

item 6. a comparison with TNFα inhibitors at 2nd line is appropriate.

4.2.4 Perspective, time horizon and discounting

The model adopts the NHS and Personal Social Services perspective. In the base-case, the model discounts costs and outcomes at 3.5%, in line with the NICE reference case, and adopts a lifetime time horizon (up to 100 years of age). Sensitivity analyses use differential discount rates, no discounting and shorter time horizons.

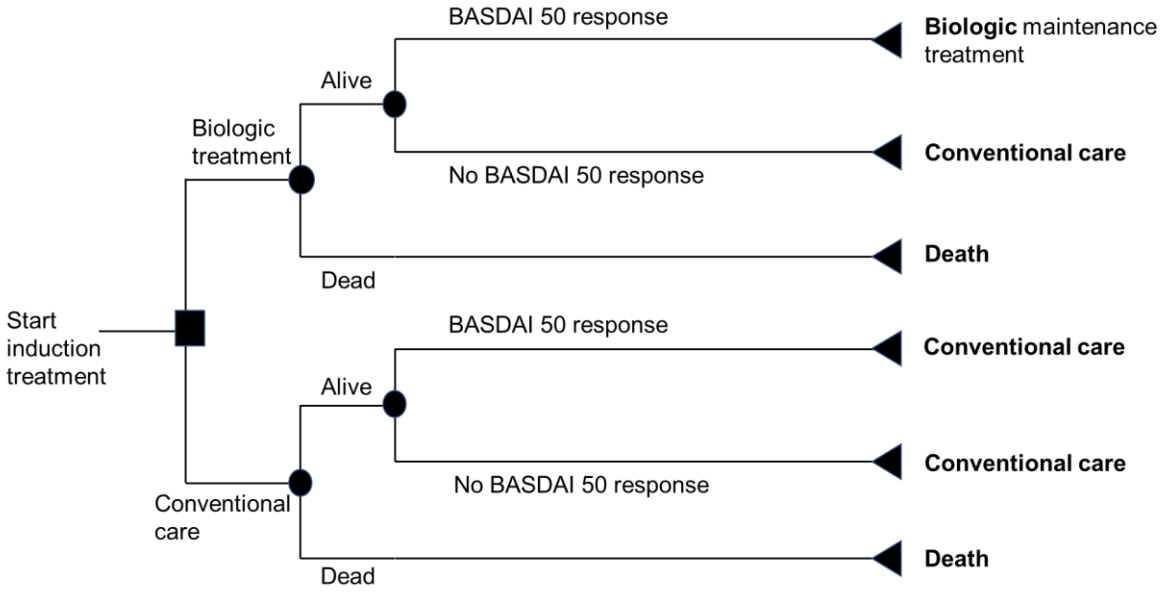
Points for critique

The ERG believes this is appropriate and has no comments on this section.

4.2.5 Model structure

The company developed a *de novo* decision model in Microsoft Excel®. The company's model consists of a short-term decision tree followed by a long-term Markov model. The decision tree, shown in Figure 7, covers the induction period until response to treatment is assessed at 12 weeks for TNFα inhibitors or at 16 weeks for secukinumab.

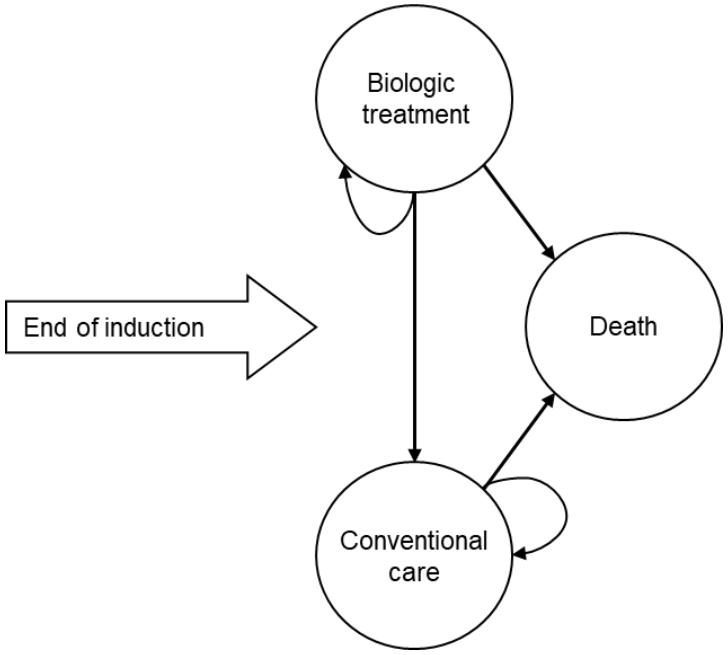
Figure 7 Structure of decision-tree covering the initial period until BASDAI50 response assessment.



Note: Based on Figure 23 of the CS.

Post-induction, a Markov model (Figure 8) with 3-month cycle length is used up to a maximum patient age of 100. Patients who responded to treatment during the induction period, enter the Markov model in the 'Biologic treatment' health state (i.e. maintenance) and remain there until they withdraw or die. In contrast, non-responders start in the 'Conventional care' health state. Patients who died during the induction period directly enter the 'Death' state.

Figure 8 Post-induction Markov model structure.



Note: Based on Figure 24 of the CS

The model tracks changes in BASDAI and BASFI scores to allow for HRQoL and costs to be based on these scores. Events in the model trigger changes to BASDAI and BASFI scores. A key event is the assessment of response, at which point both responders and non-responders are attributed changes in BASDAI and BASFI score. The improvement in score is bigger in responders compared to non-responders. The magnitude of change in these scores for both responders and non-responders depends on the treatment being received. Following the assessment of response, the BASDAI score is assumed to remain constant while on treatment. The BASFI score is assumed to increase over time on treatment, with the increase while on biologics happening at a reduced rate when compared to conventional care. The assumptions underlying changes over time are summarised in Table 63 and Figures 26 and 27 of the CS. For both BASFI and BASDAI, discontinuation is assumed to reverse the initial gain. The model assumes responders and non-responders have different baseline values for BASDAI and BASFI. Because the response rate is relative to baseline and depends on treatment, the baselines for responders and non-responders also depend on treatment. BASDAI and BASFI scores at each cycle are hence driven by the baseline BASDAI and BASFI scores, the health state the patient is in, the specific treatment received and, for BASFI, the duration of time spent on treatment.

The model structure defines the following main clinical parameters: treatment effectiveness on BASDAI50 response (further detailed in subsection 4.2.6.1); baseline BASDAI and BASFI conditioned on response (further detailed in subsection 4.2.6.2); short-term changes in BASDAI and BASFI (further detailed in subsection 4.2.6.3); long-term changes in BASFI (further detailed in

subsection 4.2.6.4), rebound in BASDAI and BASFI (further detailed in subsection 4.2.6.5), withdrawal from therapy (further detailed in subsection 4.2.6.6), mortality (further detailed in subsection 4.2.7) and adverse events (further detailed in subsection 4.2.8).

Points for critique

The model structure in the CS closely reflects the model developed in TA383,[13] which the ERG considers appropriate.

The ERG considered how the model was implemented. The base case model in the CS tracks the timing at which patients discontinue biologic treatment (and switch over to conventional care), to evaluate their BASDAI and BASFI values. However, in further calculations such as determining costs and HRQoL implications of BASDAI /BASFI impairments, the model uses average BASDAI/BASFI scores across patients discontinuing treatment at different time points. Given that the model implements a non-linear relationship between BASDAI/BASFI and costs, using the average BASDAI/BASFI scores can bias results. This was considered by the ERG:

item 7. an implementation error in the model where average scores are used to calculate costs and HRQoL.

The ERG, however, does not expected the magnitude of bias to have significant implications for cost-effectiveness.

4.2.6 Treatment effectiveness and extrapolation

The model in the CS allows treatment to affect:

- response assessed after the induction period, determined by BASDAI 50 (a 50% change from baseline in BASDAI score),
- change from baseline in both BASDAI and BASFI, and
- long-term progression in BASFI.

In the base-case that considers treatment naïve patients, treatment specific response to BASDAI 50 and changes in BASDAI and BASFI after induction were informed by evidence from the NMA (Section 3.4). The NMA model synthesises RCTs on biologics for nr-axSpA and includes data from PREVENT on treatment-naïve patients randomised to secukinumab's dosing regimen with loading and placebo, while excluding the arm of PREVENT where secukinumab is used without loading. The NMA model appropriately considers the outcomes used in the economic model together, by modelling changes in BASDAI and changes in BASFI as correlated, and by functionally relating BASDAI 50 to the underlying changes in BASDAI observed. Further, the model assumes

exchangeable treatment effects across TNFα inhibitors (a class effect), but the CS uses TNFα-inhibitor-specific shrunken estimates (see Table 49 of the CS) in the base-case decision model.

Points for critique

As highlighted above in item 4 of the ERG's critique, the ERG thinks that individual TNFα inhibitors should not each be comparators and that, instead, a single effectiveness estimate, representing the class of TNFs, should be considered.

As referred in section 3.4.2.2, the ERG considered that:

item 8. evidence from both the loading and no loading arms of PREVENT is relevant to establish the effectiveness of secukinumab.

In light of the critique in Section 3.5, the ERG believes NICE should consider the NMA results at face-value. However, the ERG considers:

item 9. significant uncertainty remains on the efficacy of secukinumab against that of TNFα-inhibitors.

As referred to in section 3.4.1 the ERG identified, and corrected, a number of errors in the data and calculations in the NMA.

4.2.6.1 Response assessment at the end of the induction period

In the base-case of the CS, response was based on the patients' BASDAI50 status at the end of the induction period, i.e. at 12-weeks for TNFα inhibitors and at 16-weeks for secukinumab. The manufacturer conducted an NMA that considers several relevant RCTs, and synthesises evidence jointly for BASDAI50, and for BASDAI and BASFI changes from baseline (Section 3.4).

Points for critique

The company's model uses BASDAI50 as a response criterion, in line with the approach taken in the model for TA383.[13] However, NICE recommends the use of TNFα inhibitors based on a composite measure of BASDAI50 or a 2-units change in BASDAI score and a reduction in the spinal pain VAS by 2cm or more[10]. These composite criteria, as highlighted in Section 0, significant increases the proportion of responders. The implications for the level of response (change from baseline in BASDAI and BASFI scores) are, however, unknown, but the ERG would expect lower changes from baseline with the composite response criteria (used in clinical practice)[38]. In their submission, the company does not provide data on the response rates based on BASDAI 50 or 2 units change in

BASDAI and a reduction in the spinal pain VAS by 2cm or more for the PREVENT trial. For these reasons, the implications to cost-effectiveness cannot be established. The ERG therefore identified as an area of significant uncertainty:

item 10. the appropriateness of the use of BASDAI50 as a response measure, which differs from the composite measure used in clinical practice.

The company provides a sensitivity analysis using ASAS40 as a response criterion. Response to ASAS40 is of a similar level to BASDAI50 and does not significantly affect cost-effectiveness.

In a previous section (3.4), the ERG described a number of corrections and adjustments to data and assumptions in the NMA model. It is of particular note that the relationships considered within the NMA model mean that baseline values and values of change from baseline with placebo affect the level of response to BASDAI 50 in conventional care considered in the economic model. Considerations around these have been detailed in Section 3.4.

4.2.6.2 Conditional baseline values for BASDAI and BASFI scores

The baseline BASDAI and BASFI scores represent the starting point for the model's cohort at the beginning of treatment. In the CS, baselines were assumed to be conditioned on response, i.e. responders to treatment are assumed to have a different baseline BASDAI and BASFI than non-responders to treatment. Baseline values conditional on response were only reported in PREVENT and in ABILITY-1 [23] (see response to ERG's clarification question B9c. For a given baseline value for the overall population, the conditional baselines should also change as the proportion of responders changes. This means the conditional baselines will also change across NMA models. The company hence derived conditional baseline scores using the following relationship, here illustrated for BASDAI:

Overall BASDAI = Responder BASDAI x % response + Non-responder BASDAI x (1-% response)

To be able to apply this relationship, the company had to further consider ratios between responder and non-responder baselines. As highlighted above, conditional values are known only for the PREVENT and the ABIITY-1 trial, and hence the company calculated ratios for these two studies. The company used the average ratio across secukinumab and adalimumab to derive the conditional baselines for the remaining TNFα inhibitors (Table 15).

Table 15: Responder / Non-responder (R/NR) ratios observed for SEC and CC in PREVENT and for ADA in ABILITY-1.

	SEC (PREVENT)	ADA (ABILITY-1)	CC (PREVENT)	average ratio*
Baseline BASDAI values for responders	[redacted]	6.21	[redacted]	
Baseline BASDAI values for non -responders	[redacted]	6.53	[redacted]	
Ratio (responder vs. non-responder)	[redacted]	0.95	[redacted]	[redacted]
Baseline BASFI values for responders	[redacted]	3.6	[redacted]	
Baseline BASFI values for non -responders	[redacted]	4.97	[redacted]	
Ratio (responder vs. non-responder)	[redacted]	0.72	[redacted]	[redacted]
Change in BASDAI for responders	[redacted]	-4.79	[redacted]	
Change in BASDAI for non-responders	[redacted]	-0.55	[redacted]	
Ratio (responder vs. non-responder)	[redacted]	8.71	[redacted]	[redacted]
Change in BASFI for responders	[redacted]	-2.75	[redacted]	
Change in BASFI for non-responders	[redacted]	-0.32	[redacted]	
Ratio (responder vs. non-responder)	[redacted]	8.59	[redacted]	[redacted]

SEC:Secukinumab, ADA:Adalimumab, CC: Conventional care

*The average ratio is calculated from the SEC and ADA R/NR ratios and the CC ratio is not included.

Points for critique

Note that the critique of the baseline BASFI and BASDAI values is undertaken above (see item 1), and hence here we focus on the use, and estimation of, the conditional baselines.

The appropriateness of the use of conditional baselines has been considered previously in TA383. In this MTA, the Assessment Group identified that the use of BASDAI50 as a response criterion means that individuals with higher BASDAI need to demonstrate a higher magnitude of absolute change in BASDAI to be classified as responders. This could mean that responders to BASDAI 50 have a lower baseline BASDAI than non-responders. In TA383, the committee noted that this suggests that people with severe disease were less likely to have a clinically meaningful benefit than those with less severe disease. In clinical practice, the response criteria would be BASDAI50 or 2 units change in BASDAI, which the committee thought would obviate differences in the baselines. Therefore, the committee preferred the use of a common baseline across responders and non-responders. In the current appraisal, and in response to the ERG's clarification question B5, the company provided a sensitivity analysis where common baseline BASDAI/BASFI scores were assumed across responders and non-responders. The ERG highlights that

item 11. whether baselines should be conditional on response is an area of uncertainty.

In the CS, the overall BASDAI and BASFI baselines are specified as a function of the probability of BASDAI 50 response which varies across the alternative NMA models. This highlights:

item 12. an error in the implementation of conditional baseline values.

The ERG considers that the approach taken to derive the conditional baseline values (based on ratios) draws on, and should hence reflect, the observed data. However, the ERG highlights that

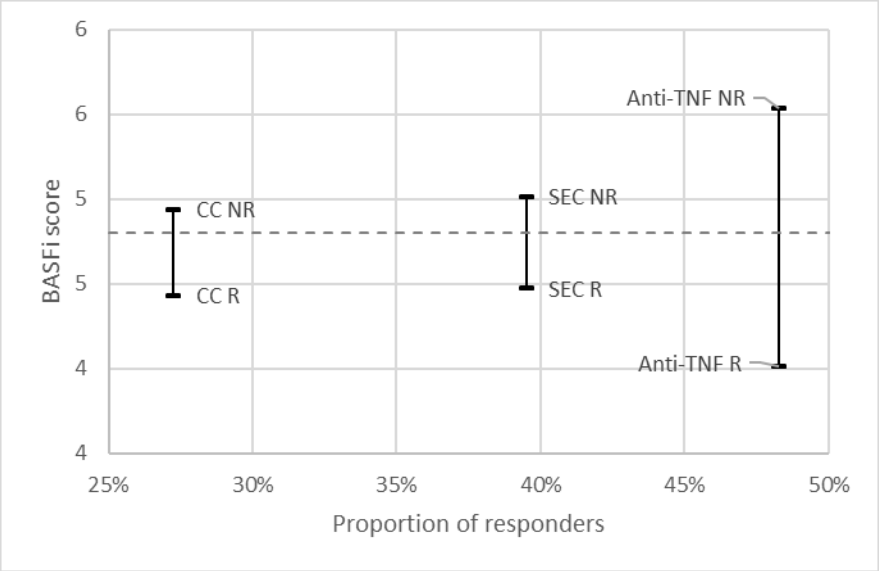
item 13. the validity of the relationship determined by the ratios (that define conditional baseline values) when used to extrapolate across response rates and across treatments is unknown.

Additionally, the ERG questions the appropriateness of using the average of the ratios of adalimumab and secukinumab to represent other TNFα-inhibitors, particularly as baseline BASFI ratios are significantly different (0.72 vs [redacted] respectively). The ERG considers:

item 14. the ratios for adalimumab may more appropriately reflect those expected of other TNFα inhibitors.

The implications of the use of the ratios to define baseline BASFI values are illustrated in Figure 9: Baselines conditional on response. Note that the conditional baselines are determined by the overall baseline value, the ratio (a lower ratio implies a bigger difference between the baseline values of responders and non-responders), and the response rate (the higher the response rate, the closer responders are to the overall baseline values and the farthest non-responders are to overall baseline values; the opposite is true for lower response rates).

Figure 9: Baselines conditional on response



4.2.6.3 Short-term BASDAI and BASFI changes

During the initial induction period, patients are assumed to experience BASDAI and BASFI improvements, the extent of which is dependent on treatment and on BASDAI50 response. In responders such an effect is assumed to sustain over the duration of treatment (as described in Section 4.2.5). In the CS, the magnitude of change in BASDAI and BASFI is also conditioned on response. To derive these, the company uses the approach described for the baseline scores (Section 4.2.6.2) and applies adalimumab's ratio to those TNFα inhibitors for which the ratio has not been observed.

Points for critique

The comment made by the ERG regarding the validity of using values conditional on response apply here (item 13) as well as the use of adalimumab's value to represent TNFα inhibitors (item 14). Note, however, that the nature of the quantity here considered means that an assumption of common values for change from baseline between responders and non-responders is unreasonable. The ERG has no further comments on this Section.

4.2.6.4 Long-term BASDAI and BASFI progression

Beyond the initial induction period, the CS assumes BASDAI remains constant for as long as the patient remains on maintenance therapy. For BASFI the CS assumes progression over time, but patients maintaining response to treatment were assumed to benefit from a reduced rate of BASFI progression. This treatment effect was applied at start of treatment and was assumed to sustain for the duration of treatment. The CS model assumes that BASFI progression is only dependent on the

modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) which relates to the progression of the radiographic disease.

The annual rate of BASFI change was calculated as follows:

Annual rate of BASFI change = BASFI change for 1-unit of mSASSS x annual rate of mSASSS change

where the change in BASFI for 1-unit of mSASSS was assumed to be 0.057 (mean = 0.057, se=0.0049) based on Landewe 2009,[39] and the post-progression annual rate of mSASSS change was assumed to be 0.69 (95% CI 0.63 to 0.75) units per year, based on the subgroup of patients with baseline mSASSS<10 reported by Ramiro *et al*.[40] Patients receiving biologic treatment were assumed to experience a reduced mSASSS change compared to conventional care, based on the relative rate of 0.42 derived from a study on AS patients.[41]

Points for critique

The approach to modelling of long-term BASDAI and BASFI in the CS was the same as in TA383. The assessment group in TA383, however, states that they originally intended to model long-term BASFI changes based on the rate of conversion from nr-axSpA to AS. This implies that patients who do not develop radiographic symptoms maintain a constant BASFI, whilst patients who develop radiographic symptoms, and hence progress to AS, are subject to the BASFI progression rate for AS patients. However, due to the lack of evidence, the more simplified assumption was made such that all patients were assumed to incur progression in BASFI, albeit at a lower rate relative to the AS population. In the current appraisal, and in response to clarifications (question B8, response to clarification questions) the company identified three recently published studies that can inform the rate of progression from nr-axSpA to AS[42-44]. The company, however, did not use this information to extend the long-term BASFI model. The ERG also identified a recent study, Protopopov 2018[5], that systematically reviews evidence of conversion to AS. Briefly, this study suggests that, based on the response criteria recommended by NICE[10], around 1% of nr-axSpA patients progress to AS every year (See Section 2.1.1). This suggests a lower progression in BASFI than what is used in the company's model, and therefore that:

item 15. long-term BASFI progression may be overestimated in the company's model.

The committee in TA383, despite the limited evidence, considered it to be biologically plausible for physical function (measured by BASFI) to continue deteriorating during TNFa-inhibitor treatment, but at a slower rate compared with the natural history of the disease (TA383 FAD 4.62). The committee in TA383 also supported the assumption that the treatment effects are sustained through the duration of treatment, despite the assessment group testing alternative assumptions (TA383 FAD 4.62). The company assumes the effect of secukinumab on BASFI progression to be equal to that of

TNFα-inhibitors. The ERG would like to highlight, however, that PREVENT offered no evidence of such an effect for secukinumab. The ERG considers that there is:

item 16. uncertainty over the treatment effect modification of long-term progression.

4.2.6.5 Rebound in BASDAI and BASFI

In the base-case, BASDAI and BASFI improvements are assumed to revert to baseline upon discontinuation of biologic therapy (i.e. 'Rebound to baseline'). The CS also explores a 'Rebound to natural history' scenario analysis where, upon discontinuation, BASFI is assumed to fall to the level that it would have been, had there been no initial response to treatment and BASFI continued progressing without any biologic treatment. The model also evaluated response in the conventional care arm after the induction period; however, patients in conventional care rebounded back to baseline/natural history in the following cycle of the model.

Points for critique

The company's base case of rebound to baseline agrees with the considerations set out in TA383 where the committee heard from the clinical experts that in clinical practice patients who lose response to TNFα inhibitors would be most likely to rebound back to their baseline scores, rather than deteriorate to a poorer state of health than they were at baseline.

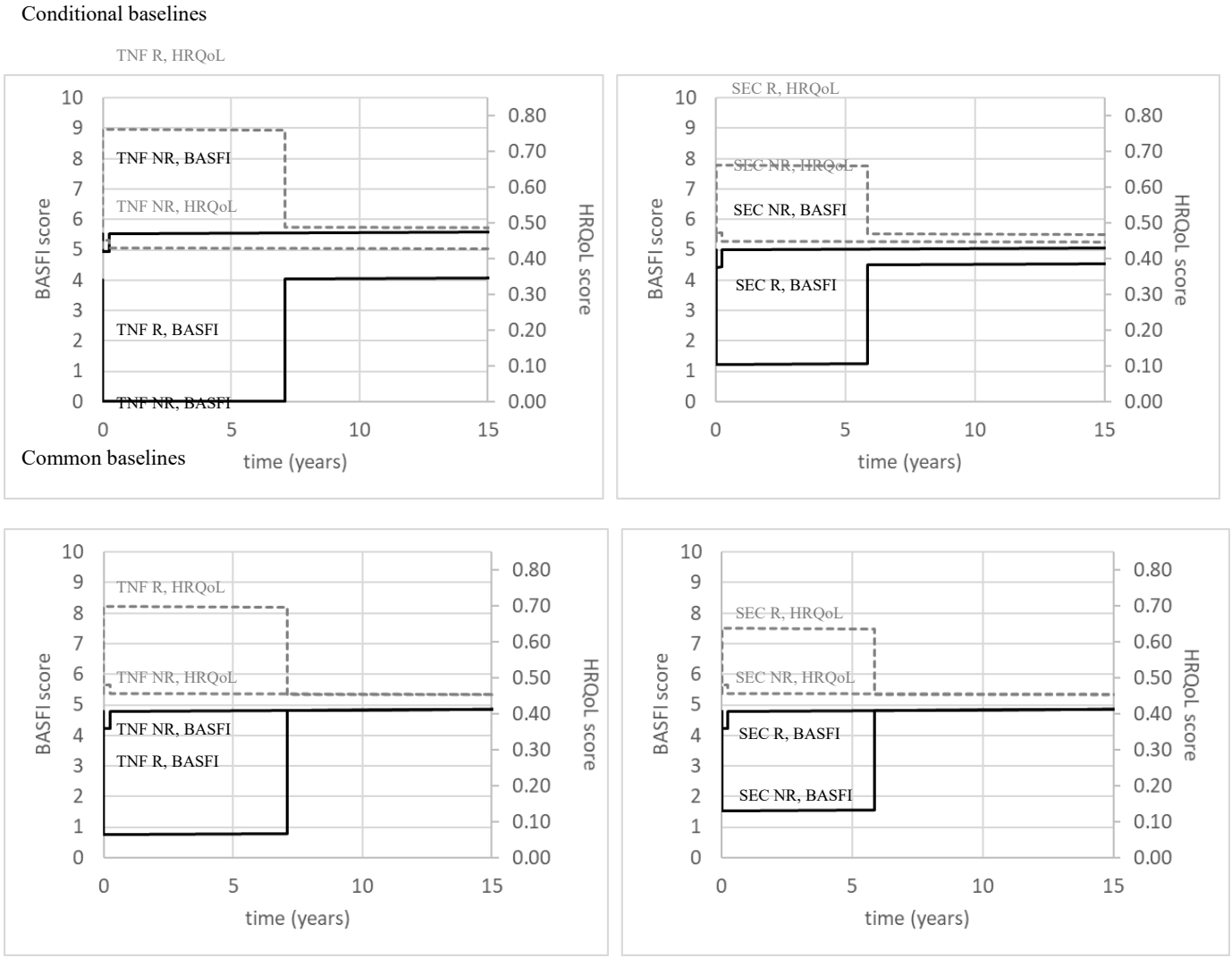
The trial evidence shows a significant level of response in placebo arms across trials (Table 7 in Section 3.3). For this reason, the company's model considers response in conventional care, and allocates an effect on BASDAI and BASFI, but assumes this to sustain only for one cycle (i.e. 3 months) after which scores rebound to baseline. However, as highlighted in Section 3.2.3.3, trial evidence show placebo-response sustains for longer than what is implemented in the company's model (reason behind such as effect remains unclear).[15] By disregarding the possibility of sustained placebo effect in the submission, the company overestimates the incremental effect of biologic treatments in relation to conventional care and underestimate its incremental costs. The ERG would therefore like to highlight as a remaining uncertainty:

item 17. the appropriateness of the rebound assumption in conventional care patients (placebo effect).

The implication of assumptions over the baseline (conditional on response or common) and rebound assumptions (item 17) on trajectories of BASFI scores and HRQoL scores are illustrated in Figure 10. The figure presents the BASFI trajectory for a patient on TNFa inhibitor (plots on the left) or secukinumab (plots on the right) when assuming conditional (top two plots) or common (bottom plots) baselines and a duration of treatment equal to the average and rebound equal to gain. The figure

highlights that progression is very slow in nr-AxSpA (item 15), and therefore it is not perceptible in the plot, and hence assumption over this are unlikely to have material impact in model outputs, including rebound assumptions. The figure highlights that assumptions over the baseline have more important implications for BASFI scores. Under treatment with a TNFα inhibitor, there is a wider difference between responders and non-responders (imposed by the smaller value of the ratio assumed for TNFa inhibitors and the different proportion of responders).

Figure 10: Examples of BASFi trajectories under conditional and common baselines



4.2.6.6 Withdrawal of biologic therapy

After the initial induction period, responders to treatment continue receiving maintenance biologic therapy until they withdraw from treatment due to loss of efficacy or adverse events. In the CS, the annual withdrawal rate is assumed to be 6%. This estimate is sourced from Pfizer's submission for

TA383 and is based on an exponential distribution fitted to 46 nr-axSpA responders of study 1031 up to week 110.[13]

Points for critique

The company does not consider recent evidence on drug survival for TNFα inhibitors in nr-axSpA. A recent study[38] looked at a UK cohort of TNF-naïve axSpA patients to evaluate long-term survival to TNFα-inhibitors. This study suggests that patients who respond initially (to the composite criteria recommended by NICE,[10]) are subject to an annual probability of withdrawal of approximately 4%. However, in this study, 611 individuals had AS (94%) and only 40 had nr-axSpA (6%). Another relevant study is the EuroSpA study[17] (summarised in Section 4.2.2) which shows drug retention rates in nr-axSpA patients that are consistently lower (84%, 73%, 64% at 6, 12 and 24 months respectively) than in AS patients (89%, 81%, 74% at 6, 12 and 24 months respectively). This contradicts the assumption of a lower withdrawal rate in nr-axSpA used as a basis to establish the 6% rate used here (originally defined in TA383) and suggests a withdrawal rates equal or above the 11% withdrawal rate assumed for AS in TA383. The retention rate for nr-axSpA in the EuroSpA study equates to an annual withdrawal rate of around 18%, but this figure is not necessarily conditional on response during the initial period. The ERG would therefore like to highlight that:

item 18. there is uncertainty over the appropriate withdrawal rate.

4.2.7 Mortality

In the CS model, nr-axSpA mortality rates are calculated by applying gender-specific standardised mortality rates (SMRs) - derived from[45]- to a Gompertz model generated by the general population mortality rates sourced from the Office of National Statistics. In line with TA383, the relative risk of mortality associated with nr-axSpA patients is calculated as 1.38 for women and 1.63 for men.

Points for critique

The ERG believes this is appropriate and has no comments on this Section.

4.2.8 Adverse events

The only adverse events taken into consideration in the model are non-melanoma skin cancer (NMSC) and serious infections, 5% of which are assumed to be tuberculosis based on[46] (See STA for AS). The treatment- specific per cycle probabilities are shown in Table 70 of the CS.

Points for critique

The ERG believes this is appropriate and has no comments on this Section.

4.2.9 Health related quality of life

The CS uses EQ-5D-5L data collected within the PREVENT trial at baseline and weeks 8, 16, 24, 52 and 76. 5L data were mapped onto the 3L valuation set developed by Dolan et. al[47] using the mapping function developed by van Hout et al.[48] Several models that related EQ-5D index scores to values of BASDAI and BASFI were fit (See Table 73 of the CS). The best performing (based on AIC and BIC) linear-mixed model used as covariates BASDAI score, BASFI score, and the interaction between BASDAI and BASFI. The selected model can be found in Table 74 of the CS.

In the cost-effectiveness analysis the CS used the best performing model in the base-case, but also explored a set of alternative utility models. These included: the model used in TA383, which also included age, sex, BASDAI^2, BASFI^2 terms; a model that used the same specification with the best performing model but was fit to the data of both the PREVENT and MEASURE1/2 trials (which included AS patients); and the model developed by McLeod.[49] The base-case model did not assume any disutility associated with adverse events and this is explored in a scenario analysis.

Points for critique

The ERG identified some minor programming errors relating to the signs and the coefficients used in the utility models in the CS; however, correcting them did not impact conclusions.

The utility model used in the company's base-case is based on the PREVENT dataset, which may not be representative given the relatively high baseline BASFI score. The model is also multilinear, which is not consistent with the non-linear model used in TA383 and with the non-linear relationship with disease costs. ***[redacted] 11 illustrates the differences in the predicted HRQoL weights for different BASFI and BASDAI values. In the figure, the lines depict combinations of BASDAI and BASFI values that return the same HRQoL score (isoquants). The more curved lines in the York model are a result of the non-linearity introduced by the higher coefficient in the interaction term between BASDAI and BASFI, which generate lower HRQoL when there is impairments to both scores than on just one of the scores, and the introduction of the square term on BASFI, which determines BASFI impairments to contribute more to HRQoL loss than BASDAI. The ERG considered

item 19. the York utility algorithm is more appropriate than the PREVENT algorithm, to reflect expected nonlinearities in HRQoL.

[redacted] 11

4.2.10 Resource use and costs

The company's model considered: i) drug acquisition costs, accounting for the duration of the induction period (12 or 16 weeks) and for biologic-specific patient access schemes (Table 16), ii) administration costs, which assumed that patients receive a one-off training session for self-administration with a hospital nurse, iii) monitoring costs (Table 77 of the CS), iv) adverse events costs (shown in Table 79 of the CS), and v) disease management costs. The latter are based on TA383, after inflating to 2019 prices, and calculated as £1,370.15 × exp (0.213 ×$BASFI$). No alternative scenarios were explored in the CS. Given that the model used the same drug acquisition costs as TA 383, in response to clarification question B9d, the company confirmed that prices also represent the current drug acquisition costs.

Table 16: Drug acquisition costs

	First 3 months	Months 4-6	Subsequent 3-months periods	Costs for 5 years of treatment
SEC	[redacted]	[redacted]	[redacted]	[redacted]

CER P	£ 0	£ 2,163	£ 2,331	£44,121
ETN	£ 2,324	£ 2,342	£ 2,331	£46,624
ADA	£ 2,465	£ 2,130	£ 2,296	£45,923
GOL	£ 3,052	£ 1,526	£ 2,289	£45,780
ETN BS	£ 2,132	£ 2,148	£ 2,139	£42,782
ADA BS	£ 956	£ 826	£ 890	£17,802

SEC: Secukinumab, CER P: Certolizumab Pegol, ETN: Etanercept, ADA: Adalimumab, GOL: Golimumab, ADA BS: Adalimumab biosimilar, ETN BS: Etanercept biosimilar

*The costs of SEC in the 'the first 3 months' column reflect the 16-weeks costs of SEC until response is assessed

To cost TNFα inhibitors when a single comparator reflecting the class was used or the model considered subsequent TNF treatment, the manufacturer used the 'market-share' information, shown in Table 17, averaged across months.

Table 17 : Market share information

Biologic treatment	Jan'19	Feb'19	Mar'19	Apr'19	May'19	Jun'19	Jul'19	Aug'19	Sep'19	Oct'19
SEC	[redacted]									
CER P	[redacted]									
ETN	[redacted]									
ETN BS	[redacted]									
ADA	[redacted]									
ADA BS	[redacted]									
GOL	[redacted]									

SEC: Secukinumab, CER P: Certolizumab Pegol, ETN: Etanercept, ADA: Adalimumab, GOL: Golimumab, ETN BS: Etanercept Biosimilar, ADA BS: Adalimumab Biosimilar

Note: submitted by the company's response to clarification question B9b

Points for critique

The ERG considered the appropriateness of market share data in costing treatment with TNFα-inhibitors. The company has not identified the source of the market share data, or described how this information was obtained, even after request for clarification (see clarification question B9b). For this reason, the ERG cannot establish the appropriateness of this source of evidence.

NICE currently recommends that, if more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen [13]. A biosimilar for adalimumab has been recently made available (late 2018), differentiating this treatment as the cheapest TNFα-inhibitor in the market (see Table 16). The ERG believes the market share data in the submission may not be representative of the expected share of use of TNFα inhibitors in first line. According to the company's data reproduced in Table 17, the market share of adalimumab biosimilar increased from 8% in January 2019 to 53% in October 2019. The uptake for adalimumab's biosimilar is expected to continue increasing. Hence, for the purpose of NICE's decision making, the ERG believes that adalimumab's use in first line is, or soon will be, extensive. The ERG believes it is reasonable to assume:

item 20. the costs of 1st use of TNFα inhibitor are likely to be closer to the cost of adalimumab's biosimilar.

4.2.11 Subgroup analyses

[redacted]

In response to the ERG's clarification question B6, the company submitted two subgroup analyses, one considering subgroups based on MRI status (i.e. MRI+ and MRI-) and another considering subgroups based on both MRI and CRP status (i.e. MRI+/CRP+, MRI+/CRP- and MRI-/CRP+). The company was not able to include TNFα inhibitors as comparators due to the lack of relevant outcome data; they provided a comparison against conventional care only based on PREVENT. The company used the model that assumed no subsequent treatments. Subgroup data from PREVENT were only available for the mixed population (i.e. both the biologic-naïve and biologic-experienced populations). Additionally, no subgroup data were available for baseline BASDAI and BASFI, and for change from

baseline in BASDAI and BASFI for responders and non-responders separately. In these subgroup analyses, therefore, the company used evidence for the overall population on baseline BASDAI and BASFI and the ratio between change from baseline for responders and non-responders. Further details are given in response to clarification (see addendum to the response to clarification questions).

Points for critique

The ERG identified that:

item 21. subgroups based on MRI and CRP status should be considered in NICE's decision making.

The ERG finds it relevant that the committee considers restricting the use of secukinumab to MRI+ patients only.

As highlighted in Section 3.2.3.1, evidence from PREVENT suggests that there is treatment effect modification according to MRI/CRP status. Specifically, in PREVENT, MRI+ and CRP + patients showed better outcomes than placebo, however the benefit of secukinumab on the MRI- and CRP + and on the MRI+ and CRP- subgroups was less clear (and non-significant in relation to placebo). It is worth noting that evidence of treatment effect modification is also available for TNFα inhibitors, namely etanercept. Whilst, due to data sparsity, the company was only able to present a comparison against conventional care,

item 22. a comparison against TNFα-inhibitors in the subgroup analyses is relevant for NICE's decision making.

4.2.12 Treatment sequencing scenario

In addition to the main analysis described above, the company also considered an exploratory scenario in which all patients who did not respond to treatment during the induction period, or responded initially but subsequently discontinued maintenance therapy, received a second-line biologic therapy. The model assumes that discontinuation of the first-line treatment was followed by a second induction period (of equal length to the first), at the end of which response was again assessed based on BASDAI50 and, conditional on response, patients entered a second Markov model (identical to the one used for 1st line). The scenario analysis presented in the original submission compared secukinumab followed by TNF with conventional care. The ERG requested, at clarification, extensions to this model that allowed evaluating:

- secukinumab followed by a TNFα-inhibitor in 2nd-line

- TNFα-inhibitor followed by secukinumab in 2nd-line
- TNFα-inhibitor followed by another TNFα-inhibitor in 2nd-line

In implementing these models, the company assumes the characteristics of the patients starting 2nd line treatment were based on the biologic-experienced subset of participants in the PREVENT trial ([redacted]), in which the average age was 43 years and 44.4% were males. The BASDAI and BASFI values at the start of 2nd line are derived by weighting the treatment-specific 1st line baselines values according to the proportion of use of each treatment as specified in the 'mixed-basket'. Also, the company assumes a reduction in effectiveness at 2nd line based on observed rates in PREVENT (see Sections B.3.3.2. and B.3.3.3. of the CS). Overall, BASDAI50 response was assumed to be reduced by [redacted], change from baseline BASDAI by [redacted], and BASFI change from baseline by [redacted].

In clarification question B3 the ERG requested further explanations on how the company considered BASFI and BASDAI scores at 2nd line treatment. In response, the company modified the 2nd line BASFI scores to account for progression in BASFI during 1st line treatment, but did not provide any results to illustrate the impact on cost-effectiveness.

Points for critique

It is important that subsequent treatments are considered in evaluating cost-effectiveness of 1st line use of secukinumab. Relevant comparators are conventional care, secukinumab followed by a TNFα-inhibitor, and TNFα-inhibitor followed by a 2nd TNFα-inhibitor (see item 5). Note that the existing literature suggests that following inadequate response to a first TNFα-inhibitor, another TNFα-inhibitor may be used in AS patients with limited losses in its treatment effect [50]. In response to the ERG's clarification question B4, the company added this option in the model (results described in Section 5.1).

The ERG therefore considered further the implementation of the sequence model in how it reflects the differential baselines across lines of treatment. The manufacturer's model does not consider that the baseline of patients that fail 1st line treatment (and are hence eligible for 2nd line treatment) differs from those that respond to 1st line treatment. This means that the modelling of the patients' BASFI and BASDAI scores is incorrect in the sequence model submitted. For this reason, the ERG believes:

item 23. the sequence model can only be used for decision making when common baselines are considered.

This implies that the ability to explore item 5 is restricted to the context of a model assuming common baselines.

The reduction in treatment effectiveness for subsequent treatments in the CS was informed by the biologic-experienced subgroup of PREVENT. However, the ERG notes that this subgroup is very small ([redacted]) and hence estimates derived from it cannot be considered reliable. Evidence regarding the reduction in the effectiveness at 2nd line exists for TNFα inhibitors based on registries in AS such as the DANBIO registry [51], which, in the absence of more reliable evidence, could be assumed generalisable to an nr-axSpA population. This register reports BASDAI50 response, median BASDAI, and median BASFI scores at baseline and at 3 months for 1st, 2nd, and 3rd line of treatment. Therefore, relative risks can be derived for reduction in BASDAI50 response, change from baseline BASDAI and change from baseline BASFI at 2nd and 3rd line, compared with 1st line (Table 18).

Table 18 Reduction in BASDAI50 response, change in BASDAI, and change in BASFI for 2nd and 3rd line treatment, in relation to 1st line treatment. Relative risks derived from the DANBIO registry [51] (PREVENT).

Line of treatment	BASDAI50 response	0-3 months change in BASDAI	0-3 months change in BASFI
2nd line (in relation to 1st line)	69% ([redacted])	64.5% ([redacted])	51.6% ([redacted])
3rd line (in relation to 1st line)	56% (NA)	41.9% (NA)	41.9% (NA)

The ERG therefore considered:

item 24. the DANBIO registry[51] provides more appropriate estimates of the reduction in effectiveness for subsequent treatments.

Given the absence of evidence for secukinumab, the ERG supports the assumption that reductions for secukinumab are of equal magnitude to those observed for TNFα-inhibitors. Note however, that this should remain as an area of uncertainty.

The ERG considered the use of secukinumab in 2nd line and beyond (e.g. at the end-of-line TNFα-inhibitors). The ERG believes the sequence model could have been a relevant vehicle to inform the cost-effectiveness of secukinumab at 2nd line, however, it has been not been implemented correctly and therefore cannot be used in this context.

The ERG would also like to note that, according to recent literature [38] and discussions with our clinical advisor, the reason for 1st line discontinuation may be important in considering the use of secukinumab at 2nd line and beyond. A patient showing no improvement in BASDAI and BASFI (i.e.

complete lack of response) to a TNFα-inhibitor at 1st line could be considered for subsequent treatment with an agent with a different mechanism of action, such as secukinumab. This suggests some role for the use of secukinumab in 2nd line. In contrast, a patient showing some level of response to TNFα-inhibitor (even if not achieving response criteria) could be considered for treatment in 2nd line with another TNFα-inhibitor before secukinumab to avoid the risk of immune-reaction due to the interruption of TNFα-inhibitors. This suggests a role for sequential use of TNFα-inhibitors, and secukinumab as last line of treatment. Recent evidence from the ATTRA registry in AS suggests that after failure of one TNFα inhibitors switching to another TNFα-inhibitor was the preferred step, and that secukinumab is primarily used as 1st or last line[52]. The CS, however, did not consider the use of secukinumab beyond second-line therapy. The ERG requested, at clarification, that the company discussed the use of secukinumab after 2 or 3 previous TNFα inhibitors (clarification question B7), but the company did not provide such discussion. Since the evidence from PREVENT suggests secukinumab has lower efficacy than TNFs in 1st line, the ERG believes the committee should consider whether it could constitute better use of NHS resources to restrict recommending secukinumab to a later positioning in the treatment pathway.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company's base case analysis, for the 1st line use of secukinumab (with no subsequent treatment considered), returned the following cost-effectiveness results

Table 19: Fully incremental analysis of 1st line use of secukinumab using only the load arm of secukinumab from PREVENT trial

Technologies	Total costs (£)	Total QALYs	Incremental costs vs baseline (£)	Incremental QALYs vs baseline	ICER incremental (£/QALY)
CC	[redacted]	[redacted]	–	–	–
SEC	[redacted]	[redacted]	£7,684	1.03	Extendedly dominated
ADA biosimilar	[redacted]	[redacted]	£8,282	1.52	£5,445
ETA biosimilar	[redacted]	[redacted]	£27,375	1.45	Dominated
CZP P	[redacted]	[redacted]	£31,008	1.67	£157,868

GOL	[redacted]	[redacted]	£33,414	1.67	£572,694

SEC: Secukinumab, CER P: Certolizumab Pegol, ETN: Etanercept, ADA: Adalimumab, GOL: Golimumab, CC: Conventional care

Note: For TNFα inhibitors with available biosimilars, cost-effectiveness figures are only presented for the biosimilars. Adapted from Table 82 of the CS. Results correspond to deterministic analyses. Adapted from Table 1 of the Addendum to clarification questions

After request for clarification, a number of further analyses were presented. Results for an analysis where the effectiveness evidence of the load and no-load arms of PREVENT have been pooled (see addendum to the response to clarification questions) is shown in Table 20, and the corresponding cost-effectiveness plane in Figure 12.

Table 20 : Fully incremental analysis for 1st line use of secukinumab using the combined load and no-load arms of secukinumab from PREVENT trial.

Treatment	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER (fully incremental)
CC	[redacted]	[redacted]	-	-	-
ADA biosimilar	[redacted]	[redacted]	£8,181	1.49	£5,491
SEC (pooled load/no load)	[redacted]	[redacted]	£8,265	1.06	Dominated
ETA biosimilar	[redacted]	[redacted]	£26,734	1.41	Dominated
CTZ	[redacted]	[redacted]	£30,521	1.64	£148,933
GOL	[redacted]	[redacted]	£33,023	1.65	£250,200

SEC: Secukinumab, CER P: Certolizumab Pegol, ETN: Etanercept, ADA: Adalimumab, GOL: Golimumab, CC: Conventional care

Note: we here omit the results for the non-biosimilar versions of ADA and ETA, as these will always be dominated by their biosimilar counterparts and hence are not relevant for decision making. Results correspond to deterministic analyses. Adapted from Table 1 of the Addendum to clarification questions

Figure 12 : Cost-effectiveness plane and efficiency frontier for 1st line use of secukinumab in the CS.

[redacted]

The results of both analyses highlight that in first line, secukinumab is [redacted] and considerably less effective (dominated) than adalimumab (biosimilar), the cheapest TNFα inhibitor available.

After request for clarification, the company submitted a further analysis where a single TNFα inhibitor comparator was included (Table 21), using market share data to cost this latter treatment. This analysis showed that secukinumab was associated with an ICER of £7.797 per QALY in relation to conventional care, and that TNFα inhibitors were cost-effective at threshold values above £25,173 per QALY. Note, however, that as highlighted in item 20 the mixed basket of TNFα inhibitors is not likely to reflect the current levels of use of the cheapest alternative, the biosilimar for adalimumab.

Table 21 : Full incremental analysis of 1st line use of secukinumab compared to a single TNFα-inhibitor (combined load and no-load arms).

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (fully incremental)
CC	[redacted]	[redacted]	-	-	-
SEC	[redacted]	[redacted]	£8,265	1.06	£7,797
TNFi	[redacted]	[redacted]	£21,355	1.58	£25,173

SEC: Secukinumab, CC: Conventional care, TNFi: TNFα-inhibitor

Note: Adapted from Table 4 of the addendum to the response to clarification questions

In response to clarifications, the manufacturer also submitted evidence from the sequence model (described in 4.2.11). As highlighted in 0, the implementation of the sequence model does not appropriately consider differential baselines for responders and non-responders. Therefore, these analyses are not considered appropriate for decision making and are shown here.

5.2 Company's sensitivity analyses

In the CS, the company undertook several sensitivity analyses for the 1st line use of secukinumab (considering evidence only of the load arms of PREVENT) – results of which are shown in Table 85 of the CS – including, amongst others, sensitivity analyses exploring alternative time horizons, alternative specifications of the NMA models, alternative rebound assumptions, and utility models. None of these analyses materially impacted cost-effectiveness.

In response to the ERG's clarification questions the company further explored a scenario where common BASDAI/BASFI baselines for responders and non-responders were used, in line with the committee's preferences in TA383. The company provided results for the sequence model (combined load and no-load data, mixed basket of TNFα-inhibitors), reproduced in Table 22.

Table 22 Fully incremental analysis for 1st and 2nd line use of secukinumab assuming common BASDAI/BASFI baselines across responders and non-responders.

	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER (fully incremental)
Sequencing model (reduced efficacy at second line for secukinumab and TNFα-inhibitors)			
SEC-> TNFi	-	-	-
TNFi -> SEC	£4,342	0.39	£11,133
TNFi -> TNFi	£8,198	0.57	£21,422

SEC: Secukinumab, TNFi: TNFα-inhibitor

Note: Results from deterministic analysis. Adapted from Table 9 of the Addendum to clarification questions. This approach assumes a single TNFα-inhibitor comparator. Reduction in efficacy at 2nd line is informed based on PREVENT data.

5.3 Company's subgroup analyses

In response to clarification (see addendum to response to clarification questions), the manufacturer submitted subgroup analyses according to patients' MRI and CRP status, which in the absence of randomised evidence on other comparators, compared only secukinumab vs conventional care and combined data from the two secukinumab arms in PREVENT (with and without loading). This

analysis assumed that the values of baseline BASDAI/BASFI are those observed for the overall population. The results are shown in Table 23.

Table 23 Secukinumab vs conventional care in the mixed population (biologic-naïve and biologic experienced), based on evidence from PREVENT trial.

Treatment	Incremental costs vs. CC	Incremental QALYs vs. CC	ICER vs. CC
CRP+ and MRI+ subgroup of mixed population			
CC	-	-	-
SEC	£9,194	1.34	£6,861
CC	-	-	-
SEC	£13,906	0.51	£27,267
CC	-	-	-
SEC	£15,045	0.52	£28,933
CC	-	-	-
SEC	£12,496	0.86	£14,530
CC	-	-	-
SEC	£13,906	0.51	£27,267

SEC: Secukinumab, CC: Conventional care

Note: Results from deterministic analysis. Adapted from Table 9 of the Addendum to clarification questions

5.4 Model validation and face validity check

The company describes the model validation process in Section B 3.10 of the CS. The ERG undertook further validation checks and identified the errors mentioned in items 8, 13, 22 and 23. No other face validity issues were identified with the model.

Compared to TA383, the company's model suggested significantly different total costs and QALYs estimates. The company attributes these to differences in the employed utility model and the fact that TNFα inhibitors were not considered as a single option. However, the ERG finds that when the utility model and the baseline BASDAI and BASFI scores are changed to those used in TA383, both total costs and QALYs become similar to those reported in TA383.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

A summary of the main issues identified and critiqued in Section 4 along with the point at which the ERG addresses the in its additional analyses is shown in Table 24.

Table 24: Summary of the main issues identified by the ERG

Critique item and description		Dealt with in the ERGs base case	Dealt with in the Other ERG analysis	Remaining uncertainty
1	BASFI baseline values in EuroSpA are likely to better reflect 1st line nr-axSpA patients	x		
2	PREVENT does not provide adequate evidence of the 2nd line use of secukinumab.		sc 13-17	x
3	unless the MA specifies otherwise, the regimen of secukinumab with no loading should be considered as the relevant intervention.		sc 8	
4	a single comparator representing the class of TNFα inhibitors should be considered.	x		
5	subsequent treatment with biologics should be incorporated in the model to establish the cost-effectiveness of 1st line use of secukinumab.		sc 12	x
6	a comparison with TNFα inhibitors at 2nd line is appropriate.		sc 13	x
7	an implementation error in the model where average scores are used to calculate costs and HRQoL.	x		
8	evidence from both the loading and no loading arms of PREVENT is relevant to establish the effectiveness of secukinumab.	x		
9	significant uncertainty remains on the efficacy of secukinumab against that of TNFα-inhibitors.			x
10	the appropriateness of the use of BASDAI50 as a response measure,			x

	which differs from the composite measure used in clinical practice.			
11	whether baselines should be conditional on response is an area of uncertainty.		sc 7, 15	x
12	an error in the implementation of conditional baseline values	x		
13	the validity of the relationship determined by the ratios (that define conditional baseline values) when used to extrapolate across response rates and across treatments is unknown.			x
14	the ratios for adalimumab may more appropriately reflect those expected of other TNFα inhibitors.	x		x
15	long-term BASFI progression may be overestimated in the company's model.		sc 9	x
16	uncertainty over the treatment effect modification of long-term progression.		sc 9	x
17	the appropriateness of the rebound assumption in conventional care patients (placebo effect).		sc 6	x
18	there is uncertainty over the appropriate withdrawal rate.		sc 10	x
19	the York utility algorithm is more appropriate than the PREVENT algorithm, to reflect expected nonlinearities in HRQoL.	x		x
20	the costs of 1st use of TNFα inhibitor are likely to be closer to the cost of adalimumab's biosimilar.	x	sc 11, 16	x
21	the sequence model can only be used for decision making when common baselines are considered.		sc 12	x
22	the DANBIO registry51 provides more appropriate estimates of the reduction in effectiveness for subsequent treatments.		sc 12, 17	x
23	subgroups based on MRI and CRP status should be considered in NICE's decision making		See section 5.3	x
24	a comparison against TNFα-inhibitors in the subgroup analyses is relevant for NICE's decision making.			x

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG made a number of changes in the company's model. These modifications were implemented in a cumulative manner for analyses 1-5; therefore, model 5 incorporates all changes described in scenarios 1-5 and corresponds to the ERG's preferred base case for 1st line use of secukinumab. Analyses 6-12 are sensitivity analyses on the ERG's base-case and have been implemented one-by-one. The ERG also conducted exploratory analyses on the use of secukinumab at 2nd line (analyses 13-17). Amongst these, analysis 13 corresponds to the ERG's preferred base-case for the 2nd line use secukinumab and analyses 14-17 pertain to additional scenarios implemented one-by-one on analysis 13.

6.1.1 Building the ERG base case

The analyses that contributed to the ERG's base-case are described below.

Note that following the critique in item 4, and in line with the committee's preferences in TA383, all analyses presented throughout consider a single TNFα-inhibitor to represent the class.

1. Correcting errors in the NMA and model.

As an initial step, the ERG corrected the errors in the company's model, identified in item 7 and item 12 . Within the timelines available, the ERG was unable to correct the issue mentioned in item 23 in the sequence model. The company's sequence model considers independent cohorts for the different lines of treatment and hence does not allow differentiating between patients that do not continue treatment after the induction period and those that respond but discontinue in the future. This would have been required to appropriately consider conditional baselines over the multiple lines of treatment.

The ERG also updated the model to consider the NMA results with the revised data (see section 3.4.2), and presents results only for a single comparator of TNFα inhibitors (item 4). As discussed in item 14, the ERG also corrected the manufacturer's model to use the responder/non-responder ratio reported for adalimumab in ABILITY-1 trial for the missing TNFα inhibitors ratios, instead of using the average of the ratios observed for adalimumab (ABILITY-1) and secukinumab (PREVENT).

2. Costing the first TNFα-inhibitor as adalimumab

Following the critique in item 20, the model has been modified to cost the first TNFα-inhibitor as the biosimilar for adalimumab.

3. Baseline BASDAI and BASFI scores based on EuroSpA, and changes from baseline for placebo based on pooled evidence from relevance trials

Following the critique in item 1 and Section 3.4, the ERG adapted the model to consider the baseline BASDAI and BASFI values reported in EuroSpA and the placebo BASDAI and BASFI changes from baseline to use values derived by pooling PREVENT, C-axSpAnd and RAPID.

4. Combining load and no-load evidence

Following the critique in item 8, the economic model here implemented used the results from the NMA that pooled the two secukinumab arms of PREVENT (secukinumab with and without loading).

5. Using York utility algorithm

Following the critique in item 19, the ERG used the 'York' utility algorithm in the model.

All the aforementioned analyses (1-5) defined in the ERG's base-case.

6.1.2 Further sensitivity analyses to the ERG's base case

The ERG undertook a number of sensitivity analyses on its preferred base-case. The following were not implemented in a cumulative manner but one-by-one.

6. Sustained placebo response

Following critique in item 17, the ERG explored two alternative scenarios where placebo response is retained beyond 3-months. In the first scenario (analysis 6a) placebo response is maintained for 52 weeks, which is the latest timepoint that PREVENT provides evidence for. In the second scenario (analysis 6b) placebo response is maintained indefinitely.

7. Common baselines

To identify the implications of the assumption over the conditional baselines (item 11), the ERG explored a scenario where common baseline BASDAI/BASFI values were assumed across responders and non-responders. This was implemented by assuming that responder/non-responder ratio for BASDAI/BASFI baselines was 1.

8. No load costs for secukinumab

Following critique in item 3, the ERG undertook a sensitivity analysis where secukinumab was costed using the regimen without loading.

9. No BASFI progression

As discussed in item 15, recent evidence (Protopopov 2018 [5]) suggests conversion to AS happens to 1% of patients per year. This suggests that BASFI progression may be lower than that considered in the company's model. Also, as identified in item 16, there is also uncertainty over the treatment effect on progression for both TNFα inhibitors and secukinumab. Given this, the ERG ran a scenario in which patients were not assumed to progress in BASFI.

10. Withdrawal rates

As discussed in item 18, withdrawal rates remain an area of uncertainty. The ERG undertook two sensitivity analyses. The first uses evidence from a UK cohort[38] that suggests an annual withdrawal rate of 4% conditional on response during the first 6 months. The second used the evidence from EuroSpA[17], which indicates an annual probability of discontinuation of 13.82% for the period between 6-18 months.

11. Market-share

To explore the impact of the cost of TNFα inhibitor treatment on the cost-effectiveness of secukinumab (item 20), the ERG explored a scenario where TNFα-inhibitors are costed based on the company's submitted market-share evidence (Table 17)

12. Considering subsequent treatment with biologics

In this analysis the ERG used the sequence model (with common baselines, in line with item 23) to explore the implications to cost-effectiveness of considering subsequent treatments (item 5). Two treatment sequences are here presented:

- secukinumab followed by TNFα-inhibitor followed by conventional care (identified in tables and figures as SEC -> TNFi -> CC), and
- TNFα-inhibitor followed by a different TNFα-inhibitor followed by conventional care (identified in tables and figures as TNFi-> TNFi-> CC).

Across all analyses, the ICERs presented reflect a comparison of the use of TNFα inhibitors vs. secukinumab, and therefore values of the ICER below the policy relevant threshold imply that first line use of secukinumab is *not* cost-effective.

The ERG noticed that the sequence model that was provided by the company in response to clarification question B3 did not account for the BASFI progression incurred at 1st line. The ERG corrected the model's 2nd line baseline BASFI to reflect the BASFI deterioration incurred during 1st line treatment. This was based on the predicted median time to discontinuation in the model (which was [redacted] cycles for the company's base case). This meant that, at the start of 2nd line treatment, BASFI was increased by [redacted].

Following the critique in item 24, the ERG here used results from DANBIO registry[51] to inform the relative risk between the 2nd line effectiveness of TNFα inhibitors and secukinumab. Also, The ERG used the costs of etanercept's biosimilar to represent the cost of the TNFα inhibitor used in second line.

6.1.3 Exploratory analyses on second line use of secukinumab

In analyses 13-17, the ERG explored the use of secukinumab in 2nd line. Note that all analyses compare the use of secukinumab with TNFα-inhibitors, identified as relevant in item 6.

13. ERG's base-case for the 2nd line use of SEC

The ERG used the company's non-sequence model and changed the baseline BASFI scores to reflect the non-responders to TNFα-inhibitors baseline BASFI (i.e. 5.537) inflated by the expected BASFI progression incurred during 1st line.

In this analysis, the ERG used evidence from DANBIO registry[51] to inform the relative risk between the 2nd and 1st line effectiveness of TNFα inhibitors and secukinumab. The ERG used conditional BASDAI/BASFI baselines and the TNFα-inhibitor was costed based on etanercept biosimilar as it is assumed that adalimumab biosimilar has been used in the previous line. It should be noted that etanercept biosimilar is considerably more expensive that adalimumab biosimilar and its cost is similar to other TNFα-inhibitors (See Table 16).

The ERG conducted sensitivity analyses (analyses 14-17), implemented one-by-one, on its base-case for 2nd line.

14. Using alternative value for the overall BASFI baseline

The ERG's explored the impact of different BASFI baselines in two scenarios; one where a lower baseline BASFI was assumed (analysis 14a), and another in which a higher baseline BASFI was assumed (analysis 14b).

15. Common BASDAI/BASFI baselines

As in analysis 7, the ERG explored a scenario where common baselines where assumed across responders and non-responders.

16. Alternative costs for the 2nd line TNFα-inhibitor

The ERG explored three scenarios where the 2nd line TNFα-inhibitor was differently priced. In the first scenario (analysis 16a), the ERG assumed that the most expensive TNFα-inhibitor (i.e. golimumab) is used at 2nd line and in the second (analysis 16b), the ERG used the market-share data that were submitted by the company. Finally, in the third scenario (analysis 16c) the ERG priced the TNFα-inhibitor according to adalimumab biosimilar to represent the scenario where the cheapest TNFα-inhibitor remains an option in 2nd line.

17. Reduction in 2nd line effectiveness based on PREVENT data

In this analysis, ERG assumed used the evidence from PREVENT trial to inform the relative risk between the 2nd line effectiveness of TNFα inhibitors and secukinumab. These were based on the pooled load and no-load arms and were 52% for BASDAI50 response, 70% for change in BASDAI, and 53% for change in BASFI.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

All ERG's analyses were only run deterministically, because the company's analysis show similar deterministic and probabilistic results, suggesting reasonable linearity within the model. A summary of results for the analyses that led to the ERG's preferred base-case (i.e. analyses 1-5) is shown in Table 25 in a cumulative manner; analysis 5 corresponds to the ERG's preferred base-case for the 1st line use of secukinumab. The results of additional sensitivity analyses, which were run one-by-one on the ERG's preferred base-case, are shown in Table 26.

In the ERG's base-case, deterministic (probabilistic) results suggest that TNFα inhibitors are associated with an ICER of £1,673 per QALY gained at 1st line, which is much lower than the usual threshold values used for decision making. Analysis 2 shows that the cost assumed for TNFα inhibitor treatment is the critical factor in determining cost-effectiveness. Other factors analysed were not as significant.

In what concerns the scenario analyses, it is worth highlighting the impact of the assumption of common baselines (analysis 7), which favoured TNFα inhibitors. The results show that the cost of TNFα inhibitor treatment is here lower than in the ERGs base case. Disease costs (linked to BASFI score) are influencing this result given the duration of treatment is equal across these analyses.

Removing the possibility of progression in BASFI (analysis 9) has a number of effects but, overall, seems to benefit TNFα inhibitors. Sensitivity analysis 10 show that higher values for the withdrawal rate favoured secukinumab and lower values favoured TNFα inhibitors. The base-case, analyses 10a and 10b, retrieve a mean duration of treatment for TNFα inhibitors of, respectively, 7.10, 9.29 and 3.48 years, and a mean duration of treatment on those that respond of 14.2, 18.75 and 6.69 years. For secukinumab, these analyses establishes a mean duration of treatment of 5.86, 7.65 and 2.90 years respectively (note that the mean duration on those that respond is equal to that of TNFα inhibitors).

The inclusion of a subsequent treatment in the common baseline model (implemented using the sequence model) worsens the cost-effectiveness of TNFα inhibitors from dominating (in analysis 7) to presenting an ICER of £12,102. Note that the costs of the 1st line TNFα inhibitor are assumed to be much lower than the 2nd line TNFα inhibitor (assumed to be those of etanercept's biosimilar). Critically, differences lie again on the costs of TNFα inhibitor treatment and not on its effectiveness in relation to secukinumab. Whilst the costs of 1st line are unchanged, the introduction of a costly 2nd line treatment with a biologic imposes costs to the secukinumab sequence of £83,252 and to the TNF sequence of £92,422. The 2nd line TNF costs in the secukinumab sequence are lower as this has been costed using adalimumab, whilst the 2nd line TNF costs in the TNF sequence have been costed using etanercept. The duration of second line treatment is slightly shorted in the TNF sequence (0.700 years) than in the secukinumab sequence (0.717 years).

Finally, results of exploratory analyses regarding the use of secukinumab in 2nd line are shown in Table 27. In the ERG's preferred base-case (analysis 13), deterministic results suggest that TNFα inhibitors are associated with an ICER of £43,312 per QALY gained which is above the usual thresholds values used for decision making. The high ICERs are driven by the high cost of the 2nd line TNFα inhibitor, which is costed based on the etanercept biosimilar (adalimumab's biosilimar is assumed to have already been used in 1st line). This is also supported by the results of analysis 16b, which uses the company's market share data and hence includes 33.5% of the adalimumab biosimilar leading to an ICER of £26,509 per QALY gained and analysis 16c, where TNFα inhibitors dominate because it is assumed that adalimumab biosimilar has not been used at 1st line and remains as an option in 2nd line. Results are robust across all other sensitivity analyses.

[redacted] 25

	Discounted costs			Discounted QALYs			ICER (1st line use of SEC) (TNFi->CC Vs SEC->CC)
	SEC -> CC	TNFi ->CC	CC	SEC -> CC	TNFi ->CC	CC	
CS base-case (1st line use, load dosage)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,632 (for TNFi)
1. CS base-case, correcting model errors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,310 (for TNFi)
2. 1 + Costing TNFi based on ADA BS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,221 (for TNFi)
3. 2 + Baseline values based on EuroSpA[17] and change values for placebo based on pooling across relevant trials	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,015 (for TNFi)
4. 3 + pooled secukinumab arms of PREVENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,447 (for TNFi)
5. 4 + York utility algorithm **(ERG's PREFERED BASE-CASE)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,673 (for TNFi)

SEC: Secukinumab, CC: Conventional care, TNFi: TNFα-inhibitor, ADA BS: Adalimumab biosimilar

Note: ICERs below £20,000 indicate that using a sequence of TNFα inhibitors is cost-effective against using SEC. All results correspond to deterministic analyses.

[redacted] 26

Analysis	Discounted costs			Discounted QALYs			ICER (1st line use of SEC)
	SEC ->CC	TNFi ->CC	CC	SEC ->CC	TNFi ->CC	CC	ICER (**SEC**-> CC vs **TNFi**-> CC)
5. ERG's base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,673 (for TNFi)
6. Sustained placebo response							
6a. Sustained up to week 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,673 (for TNFi)
6b. Sustained indefinitely	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,673 (for TNFi)
7. Common BASDAI and BASFI baselines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TNFi dominates
8. Using No-load costs for SEC (Depending on marketing authorisation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,700 (for TNFi)
9. No BASFI progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,286 (for TNFi)
10. Withdrawal rates							
10a. Yahya[38] 4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£199 (for TNFi)
10b. Eurospa[17] 13.82%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,824 (for TNFi)
11. Company's market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,811 (for TNFi)
	SEC ->TNFi ->CC	TNFi ->TNFi ->CC	CC	SEC ->TNFi ->CC	TNFi ->TNFi ->CC	CC	ICER (**TNFi**->TNFi->CC vs **SEC**->TNFi->CC)
12. Treatment sequence with common baselines. Note that 2nd TNFi is costed as etanercept biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,102 (for TNFi sequence)

SEC: Secukinumab, CC: Conventional care, TNFi: TNFα-inhibitor, ADA BS: Adalimumab biosimilar, ETA BS: Etanercept biosimilar

Note: ICERs below £20,000 indicate that using a sequence of TNFα-inhibitors is cost-effective against using SEC. All results correspond to deterministic analyses.

[redacted] 27

Analysis	Discounted costs			Discounted QALYs			ICER (1st line use of SEC)
	TNFi ->TNFi ->CC	TNFi ->SEC ->CC	CC	TNFi ->TNFi ->CC	TNFi ->SEC ->CC	CC	ICER (**TNFi->SEC**-> CC vs **TNFi->TNFi**-> CC)
13. ERG's base-case for 2nd line use of SEC (costing 2nd TNFi as ETA BS). Reduction in effectiveness based on DANBIO registry[51]. Overall baseline based on non-responders to anti-TNF baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,312 (for TNFi)
14. Different BASFI baseline values							
14a. Lower overall BASFI baseline (i.e. 5.948 - 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,362 (for TNFi)
14b. Higher overall BASFI baseline (i.e. 5.948 + 1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,799 (for TNFi)
15. Common baselines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,466 (for TNFi)
16. Costing 2nd lines TNFi based on:							
16a. the most expensive TNFi (i.e. GOL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,508 (for TNFi)
16b. on company's market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,509 (for TNFi)
16c. ADA BS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TNFi dominates
17. Reduction in effectiveness is based on PREVENT evidence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,883 (for TNFi)

SEC: Secukinumab, CC: Conventional care, TNFi: TNFα-inhibitor, ADA BS: Adalimumab biosimilar, ETA BS: Etanercept biosimilar, GOL: Golimumab

Note: ICERs below £20,000 indicate that using a sequence of TNFα-inhibitors is cost-effective against using SEC at 2nd line. All results correspond to deterministic analyses.

6.3 Conclusions of the cost effectiveness Section

The company submitted a *de novo* model which was largely based on the York model developed for TA383 to consider the use of TNFα inhibitors for AS and nr-axSpA. The company searched but did not identify any previous cost-effectiveness analyses for secukinumab in nr-axSpA and consequently most model parameters (excluding relative effectiveness parameters) were assumed equal to those in the York model in TA383. The ERG deems that the submitted evidence reflects the decision problem defined in the final scope.

However, the ERG does not consider ICER estimates provided in the company's base case to accurately reflect the cost-effectiveness of the use of SEC 150mg in 1st line for the treatment of nr-axSpA patients. There are four main reasons for this, additional to some implementation errors that have been corrected by the ERG. First, patients enrolled in PREVENT had a baseline BASFI score which was higher than other nr-axSpA trials and a recent analysis of several registries (see item 1). Second, the company does not include subsequent treatments in assessing the cost-effectiveness of 1st line use of secukinumab, which is not reflective of clinical practice (item 5). Third, the company's base case only considers evidence for the PREVENT arm where secukinumab was used with loading, ignoring the evidence of the arm where secukinumab was used without loading (item 8). Given that outcomes at 16 weeks are very similar between the two arms, by ignoring part of the evidence the CS's base case does not accurately reflect uncertainty in the treatment effect of secukinumab and its comparison with TNFα inhibitors. Finally, the company does take into account that the recent introduction of the first biosimilar for adalimumab, which is as effective as the other TNFα inhibitors and considerably less expensive, distinguishes it as a clear option amongst TNFα inhibitors (item 20). Treatment with adalimumab's biosimilar is cheaper than treatment with secukinumab. The ERG's analyses considering these aspects suggest that 1st line use of secukinumab may not represent a cost-effective use of resources.

However, there are a number of remaining uncertainties and amongst the items listed in Table 24 the ERG wold like to highlight four areas are of primary importance. First, whilst the results of the NMA were taken at face-value, there is considerable uncertainty on how the effectiveness of secukinumab compares to that of TNFα inhibitors for nr-axSpA patients. [redacted] Third, all the analyses presented here use a BASDAI50 criteria for response, instead of the composite response criteria used in clinical practice,

which define response as BASDAI50 or a reduction of two units of BASDAI and a reduction in spinal pain VAS by 2 cm or more[10]. Based on recent evidence from a UK cohort[38], the composite response criteria may classify considerably more patients as responders, and consequently extend the use of the treatments to patients that do not respond as well. Given no evidence on the extent of response to these criteria was submitted, the impact on cost-effectiveness is unknown. Finally, it remains uncertain whether baseline BASDAI and BASFI should be conditioned on response and the impact of this on cost-effectiveness in a model where subsequent treatments are considered is also unknown. Whilst conditional baselines have been justified on the basis of the use of the relative BASDAI 50 criteria, the ERG believes composite response criteria used in clinical practice is likely to diminish such an effect.

The company also submitted evidence on second line use of secukinumab, based on the subgroup of experienced participants in the PREVENT trial. This subgroup was however very small and the ERGs does not consider these analyses to be suitable for decision making. The ERG conducted exploratory analyses, on the use of secukinumab 2nd line. These show that secukinumab may be cost-effective if 2nd line TNFα inhibitor treatment is not costed at the price of adalimumab's biosimilar. However, note that underlying these analyses are a number of assumptions, such as the extent of reduction in effectiveness (at an equal level) in both secukinumab and TNFα inhibitor, uncertainty over the BASFI and BASDAI scores at the start of 2nd line treatment and the fact that reason for discontinuation is not considered here. These results should therefore be interpreted with caution.

Finally, it should be noted that, given the different mechanism of action, secukinumab might prove a valuable treatment alternative for patients who show complete lack of response to TNFα inhibitors in a previous line of treatment. However, the company did not submit any evidence on this group of patients and therefore the effectiveness and cost-effectiveness of secukinumab in this subgroup cannot be established.

In conclusion, the ERG's results indicate that secukinumab may not be cost-effective in relation to TNFα inhibitors in 1st line. The cost-effectiveness of secukinumab may improve if its use is restricted to MRI+ patients, as there is some evidence (although uncertain) that this treatment may not be cost-effective in MRI- patients. Secukinumab may be cost-effective in 2nd line, after the use of the least expensive TNFα inhibitor in 1st line. There are a number of limitations in the evidence submitted that make conclusions tentative, namely the fact that the response measure modelled does not reflect the response measure used in clinical practice.

7 END OF LIFE

The company does not claim that the end of line criteria are met within the appraisal of secukinumab. The ERG agrees with this position and notes that the short-life expectancy is not met, with patients living on average considerably longer than two years

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9 APPENDICES

[redacted]28[redacted]

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* 95% Credible Intervals

13

9.1 Sensitivity Analyses conducted by ERG

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[redacted]	[redacted]	Mean	[redacted]
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		95% CrI	[redacted]
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* SD of mean class effect

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		95% CrI	[redacted]	[redacted]

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Secukinumab for treating non-radiographic axial spondyloarthritis [ID1419]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Monday 9 March 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Key issues

Issue 1 Misreporting of primary outcome results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11 In the sentence [redacted]" the numerical values are not correct as these relate to a secondary outcome. The primary outcome of the study was ASAS40 response in TNF-alpha naïve patients at Week 16 whereas the presented results are for all patients at Week 16.	Please change to [redacted]" Alternatively, keep the numbers as they are but explain that these are results of the secondary outcome ASAS40 response in all patients at Week 16.	This should be corrected for accuracy.	The sentence has been amended and now states that the result relates to all patients.

Issue 2 MRI/CRP subgroup results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 The ERG state [redacted]	Please amend to [redacted]"	In the CRP+/MRI- and CRP-/MRI+ subgroups there was a [redacted]	The ERG does not consider this to be a factual inaccuracy, and thinks that our original wording is reasonable, given the data in Table 4 of the ERG report.

[redacted]			
Page 98 The ERG states that "PREVENT data suggests secukinumab effectiveness may be more comparable to that of TNFα inhibitors in patients that are MRI+, and that the benefit of secukinumab on MRI- patients is very limited."	Please replace with: "PREVENT data suggests secukinumab effectiveness may be more comparable to that of TNFα inhibitors in patients that are MRI+, and that the benefit of secukinumab on MRI- patients is very limited. This may also be the case for TNFα inhibitors, although this is not known with certainty as data for TNFα inhibitors are severely limited"	The current statement implies a greater level of certainty in the results of subgroup analyses than is available and that secukinumab differs from TNFα inhibitors in this respect, which is unknown due to lack of subgroup data for TNFα inhibitors.	Not a factual inaccuracy

Issue 3 Comparison of PREVENT with other trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 The ERG state that they "found no consistent pattern of baseline characteristics or placebo group rates that differentiated PREVENT from other trials"	Please amend to "found no consistent pattern of baseline characteristics or placebo group rates that differentiated PREVENT from other trials, although baseline BASFI, BASDAI and mean age were higher in PREVENT than any other trials (Figure 3, page 78, Appendix D of the CS)"	These statements may be misleading, as data presented in the CS show that there were consistent patterns of baseline characteristics and placebo group rates that differentiated PREVENT from other trials. On Page 13 of the ERG report the ERG state that the population in PREVENT "manifests itself by a high value of BASFI indicating high	The ERG considers that baseline rate is only evidently higher for BASFI. We have amended to: …found no consistent pattern of baseline characteristics or placebo group rates that differentiated PREVENT from other trials, although baseline BASFI was higher in PREVENT.

Page 36 The ERG state “although placebo response rates do vary across trials, they were also high in some of the other trials, and so were not an issue exclusive to PREVENT”	Please amend to “although placebo response rates do vary across trials, they were also high in some of the other trials, and so were not an issue exclusive to PREVENT. It is the case, however that placebo response rates were higher in PREVENT than any other trial in the comparison for 3 out of 4 key outcomes: ASAS40, BASDAI CFB, BASFI CFB (Figure 11, page 89 of the CS)”	functional impairment in the sample recruited and the high and sustained placebo response observed”, which appears to contradict the statement on Page 12 that no consistent patterns were observed.	Section has been amended to read “although placebo response rates do vary across trials, they were also high in some of the other trials. However, placebo response rates were notably higher in PREVENT for ASAS40 and BASFI (Figure 11, page 89 of the CS).

Issue 4 Treatment rankings

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 The ERG states that “The Bayesian rankings of treatments (requested by the ERG) consistently ranked secukinumab as the least effective of the active treatments (i.e. consistently in 5th place, ahead of placebo)”	Please amend to “The Bayesian rankings of treatments (requested by the ERG) placed secukinumab in a range of positions, although secukinumab most frequently ranked as the least effective of the active treatments (i.e. in 5th place ahead of placebo)”	We do not believe that it is accurate to say secukinumab consistently ranked in 5th place, when on two rankograms (BASFI change from baseline with all treatments considered different, both fixed and random effects) secukinumab’s most likely position was first. In seven others secukinumab was most likely to rank 2nd, 3rd or 4th.	The ERG stands by its interpretation of the rankograms, but we have edited: “consistently ranked” to “generally ranked”

Issue 5 Inclusion of the adalimumab biosimilar price

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14 The ERG states that "the cost-effectiveness evidence presented by the manufacturer fails to acknowledge the recent introduction of the adalimumab biosimilar, which is as effective as other TNFα inhibitors and considerably less expensive, and that this treatment is becoming increasingly used for first line treatment."	Please remove this statement to avoid misinterpretation of the company's submitted analysis.	This statement is incorrect as the submitted model included adalimumab biosimilar as both a comparator at first line, and as one of the 'mixed basket' of second-line therapies in the sequencing scenario. The cost of adalimumab biosimilar is reflective of the current national tender price published by NHS England in April 2019, for which there is no case precedence in published NICE guidance. This cost is included in both base-case and sequencing scenarios presented in the economic evidence, and is therefore accounted for throughout the CS.	The ERG report has been amended and now reads: "The cost-effectiveness evidence presented by the manufacturer fails to acknowledge that adalimumab's biosimilar, which is as effective as other TNFα inhibitors and considerably less expensive, is becoming increasingly used for first line treatment"

Issue 6 Potentially misleading summary of PREVENT trial results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 56 The sentence "However, the PREVENT trial in nr-axSpA showed consistently lower effectiveness for secukinumab when compared to placebo across several outcomes" suggests that secukinumab was less effective versus placebo in PREVENT.	Please amend to "However, the PREVENT trial in nr-axSpA showed consistently lower effectiveness for secukinumab versus placebo across several outcomes when compared with secukinumab trials in AS" – if this is the intended meaning of the sentence.	The current wording could be interpreted to mean that SEC is less effective than placebo in nr-axSpA. Page 11 of the ERG report is correct in stating [redacted]	Amended as suggested.

		[redacted]	

Issue 7 Incorrect description of secukinumab licensed dosing schedule

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61 The ERG states that "secukinumab is administered at weeks 0, 1, 2, 3, 4 followed by one dose every four weeks", which doesn't align with the license or the dosing schedule described in the CS and model.	Please change from "one dose every four weeks" to "one dose every month".	This should be corrected to accurately reflect the licensed posology of secukinumab.	The ERG changed the report according to the company's proposed amendment

Issue 8 Combining Load and No- Load data

Description of problem	Description of proposed amendment	Justification for amendment	ERG report
Page 62 The ERG states that "the submission shows no evidence of a difference in clinical outcomes between the load and no-load regimens across all primary and secondary outcomes"	Please replace with: "the submission shows no evidence of a clear difference in clinical outcomes between the load and no-load regimens across primary and secondary outcomes, although there was a consistent trend towards numerically higher efficacy responses with the 'Load' regimen within the first 16 weeks."	The current statement may be misleading, as the Novartis regulatory submission to the EMA defines the secukinumab trial arms as two separate intervention groups; pooling of the two secukinumab interventions therefore violates rules of evidence synthesis methodology.	Not a factual inaccuracy
Page 62 The ERG states that "unless the MA specifies otherwise, the	Please replace with: "Although the EMA license is expected to be for the load regimen, the ERG considers that the regimen with no	This statement may be misleading, as the licensed posology for secukinumab in nr-axSpA is	Not a factual inaccuracy

regimen of secukinumab with no loading should be considered as the relevant intervention"	load should be considered as a relevant intervention in the event that loading is not specified in the license."	anticipated to align to the AS licensed posology and hence the 'No Load' regimen is not expected to be licenced in England and Wales.	
Page 89 The ERG uses efficacy data based on pooled load and no-load data, but assumes costs based on the load regimen	It seems inconsistent to use weighted average efficacy inputs but only Load regimen costs. We suggest that if efficacy is based on combined load and no- load data, then it may be more appropriate to do the same for costs.	Costs and efficacy data used in the ERG base-case are currently inconsistent with each other.	Not a factual inaccuracy

Issue 9 Availability of data in biologic-experienced patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63 The ERG state that "a comparison with TNFα inhibitors at 2nd line is appropriate"	Please replace with: "a comparison with TNFα inhibitors at 2nd line would be considered appropriate although is limited by lack of comparative efficacy data for TNFα inhibitors at 2nd line."	The current statement implies that sufficient data are available to perform a robust comparison against TNFα inhibitors.	Not a factual inaccuracy
Page 81 The ERG state "given the absence of evidence for secukinumab, the ERG supports the assumption that reductions for secukinumab are of equal magnitude to those observed for TNFα-inhibitors"	Please replace the current statement with: "based on PREVENT data for secukinumab and registry data for TNFα inhibitors, the ERG supports the assumption that reductions for secukinumab are of equal magnitude to those observed for TNFα-inhibitors."	Both PREVENT and DANBIO are associated with limitations as sources of the reduction in efficacy at second-line for the technologies considered in this appraisal; however, PREVENT, a randomised controlled trial, is expected to represent the best available evidence for the reduction in efficacy for secukinumab.	Not a factual inaccuracy

Issue 10 Use of BASDAI50 as the measure of response

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68 The ERG states that "the ERG therefore identified as an area of significant uncertainty the appropriateness of the use of BASDAI50 as a response measure, which differs from the composite measure used in clinical practice"	Please replace with: "the ERG therefore identified as an area of significant uncertainty the appropriateness of the use of BASDAI50 as a response measure, which differs from the composite measure used in clinical practice. However, it is recognised that this approach is consistent with previous appraisals and represents the only possible approach given the available comparator data."	The current statement implies that alternative approaches were possible.	Not a factual inaccuracy

Issue 11 Committee views on conditional baselines in TA383

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69 The ERG state that "the committee preferred the use of a common baseline across responders and non-responders"	Please replace with: "although the committee in TA383 preferred the use of a common baseline in responders and non-responders, the Assessment Group's base-case model, which included conditional (i.e. not common across responders and non-responders) baselines, was ultimately used for decision-making."	Although the committee in TA383 had a preference for common baselines for BASDAI/BASFI in responders and non-responders, the York model's assumption of conditional baselines was used to inform the final guidance.	Not a factual inaccuracy

Issue 12 Lack of clarity in reporting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 70 The ERG states that "this highlights an error in the implementation of conditional baseline values"	Please clarify the error in the implementation of conditional baseline values.	It is not currently clear what the error in the implementation of conditional baseline values is. Whilst Novartis recognises that this may not be a factual inaccuracy on the part of the ERG, nevertheless, we are unclear on what the error in the implementation of conditional baseline values is, and some further detail would be extremely helpful.	The ERG report now reads "In the CS, the overall BASDAI and BASFI baselines are specified as a function of the probability of BASDAI 50. Given that BASDAI 50 varies with the NMA model, the baseline BASDAI and BASFI also vary. The ERG thinks that the baselines should be representative of the nr-axSpA population and should not depend on the chosen NMA model."
Page 80 The ERG state that "the sequence model can only be used for decision making when common baselines are considered"	Please clarify the rationale for this statement.	Whilst Novartis recognises that this may not be a factual inaccuracy on the part of the ERG, nevertheless, we are unclear on how this conclusion has been reached. Some further detail would be extremely helpful.	The ERG report has been amended and now reads as follows "The manufacturer's model does not consider that the baseline of patients that fail 1st line treatment (and are hence eligible for 2nd line treatment) differs from those that respond to 1st line treatment. Instead, all patients initiating 2nd line therapy (independently of whether they responded or not to 1st line treatment) are assigned the same baselines only conditioned on their response

			in 2nd line. This means that the modelling of the patients' BASFI and BASDAI scores is incorrect in the sequence model submitted and the company's model can only be used when common baselines are considered"

Issue 13 Assumption that adalimumab biosimilar is representative of the class of TNFα inhibitors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 79 The ERG state that "the costs of 1st use of TNFα inhibitor are likely to be closer to the cost of adalimumab's biosimilar"	Please replace with: "The costs of 1st line use of TNFα inhibitor are expected to lie somewhere between the cost based on current market share and costs assuming 100% market share for adalimumab biosimilar, which is costed at the current national reference price (for the financial year 2019-2020)"	The current statement may imply that adalimumab biosimilar is used in 100% of patients and that the current reference price is available in perpetuity.	Not a factual inaccuracy
Page 80 The ERG states that "relevant comparators are conventional care, secukinumab followed by a TNFα-inhibitor, and TNFα-inhibitor followed by a 2nd TNFα-inhibitor"	Please add after this statement: "The ERG's listed comparators differ from the company's and from those listed in the final scope, and effectively compares secukinumab against adalimumab biosimilar, only."	The current statement does not make clear that etanercept, golimumab and certolizumab pegol have effectively been removed from consideration as comparators.	Not a factual inaccuracy

Issue 14 Uncertainty surrounding the ERG's baseline BASDAI and BASFI scores

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 89 The ERG's base-case uses baseline BASDAI and BASFI scores from EuroSpA and relevant trials to calculate the change from baseline in the placebo arm.	Please add the following statement: "Although the ERG considered these sources to be most applicable to their base-case analysis, the baseline scores and pooled change from baseline values used by the company were informed directly by the NMA, and may therefore be subject to less heterogeneity/uncertainty."	This proposed approach invalidates the NMA options available in the cost-effectiveness model, which relate specifically to the baseline characteristics of the modelled population.	Not a factual inaccuracy

Issue 15 Use of adalimumab biosimilar in both first and second line

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 93 The ERG state that "in the third scenario (analysis 16c) the ERG priced the TNFα inhibitor according to adalimumab biosimilar to represent the scenario where the cheapest TNFα-inhibitor remains an option in 2nd line"	Please either remove this scenario or add the following statement: "It is acknowledged that this scenario is not plausible in clinical practice".	Adalimumab biosimilar is not expected to be used as a second-line treatment following first-line adalimumab biosimilar.	Not a factual inaccuracy

Issue 16 Positioning of secukinumab in the treatment pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 99 The ERG concludes that "given the different mechanism of action, secukinumab might prove a valuable treatment alternative for patients who show complete lack of response to TNFα inhibitors in a previous line of treatment."	Please replace the underlined text with "who respond inadequately."	The current statement does not reflect the fact that biologic-experienced patients in PREVENT included those who had experienced an inadequate response to previous or current treatment with a TNFα inhibitor given at an approved dose for at least 3 months prior to randomisation, or had been intolerant to at least one administration of a TNFα inhibitor. In other words, the biologic-experienced population in PREVENT contains a mix of those who did not respond to a TNFα inhibitor at 3 months, those who initially responded and subsequently discontinued, and those who are intolerant to TNFα inhibitors.	Not a factual inaccuracy

Minor issues

Issue 17 Inaccurate description of ASAS criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17 The ERG state that "To be classified as nr-axSpA via the clinical arm of the criteria, patients must test positive for the HLA-B27 genetic marker and also have at least **three** of the aforementioned SpA features".	Please amend to "To be classified as nr-axSpA via the clinical arm of the criteria, patients must test positive for the HLA-B27 genetic marker and also have at least **two** of the aforementioned SpA features"	This does not impact the rest of the report but should be corrected for accuracy.	Thank you for spotting this. Amended as suggested.

Issue 18 No load comparison provided in response to ERG questions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 20 The ERG state that "The company's submission compares secukinumab 150mg once a month, both with or without loading doses in the first month, with the aforementioned recommended TNFα inhibitors at their licensed doses"	Please specify that comparison with TNFα inhibitors using no load was provided in response to ERG clarification questions rather than in the submission. "The company's ***response to clarification questions*** compares secukinumab 150mg once a month, both with or without loading doses in the first month, with the aforementioned recommended TNFα inhibitors at their licensed doses"	This amendment will signpost the reader towards the correct place to find these data.	Amended as suggested

Issue 19 Use of ASAS as trial eligibility criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25 The ERG states “In light of these issues the ERG is also concerned about the diagnostic eligibility criteria (CS, p35) which are: “Diagnosis of axSpA according to ASAS criteria”. The ASAS criteria are not meant to be diagnostic, and it seems unclear whether enough attention was given to rule out other conditions, before arriving at a diagnosis of nr-axSpA.”	Please amend as follows; “In light of these issues the ERG is also concerned about the diagnostic eligibility criteria (CS, p35) which are: “Diagnosis of axSpA according to ASAS criteria”. ***Although most of the comparator trials in nr-axSpA also used ASAS criteria to select eligible patients***, these are not meant to be diagnostic, and it seems unclear whether enough attention was given to rule out other conditions, before arriving at a diagnosis of nr-axSpA.”	The current wording implies that eligibility criteria in PREVENT differed greatly from other trials in nr-axSpA. However, most of the comparator trials had similar eligibility criteria. Furthermore, X-rays and MRI were centrally read by world-class experts to ensure the screening tool provided clarity regarding the diagnosis and ensured a clean nr-axSpA study population, without dilution by mechanical back pain patients or AS patients.	Not a factual inaccuracy.

Issue 20 Duplicated text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29 The following paragraph is a duplicate of a paragraph on Page 28: “[redacted]	Please remove the duplicated paragraph and add cross-reference if necessary.	This will improve readability of the report.	Duplicate text deleted.

[redacted]			

Issue 21 Lack of references and broken cross-reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 29 Two statements are unsupported by references: "The ERG identified data in a recent paper of a UK cohort of patients with axial spondyloarthritis (mostly patients with AS, but some with nr-AxSpA) which indicated that a BASDAI 50 response and/or a two or more points reduction was achieved by 409/508 (81%) patients, whereas a BASDAI 50 response was only achieved by 275 (54%)" "There is also evidence to show that placebo effects can last much longer than a few weeks or months" At the end of the first paragraph there is also a broken cross reference "(Section 0)".	Please provide references for the statements and fix the broken cross-reference.	This will improve the readability of the report and allow the reader to examine the source material.	References added for both

Issue 22 Incorrect reference and rationale for using multiple sources

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42–43 The following line contains an incorrect reference "However, baseline BASDAI and the corresponding standard deviation (SD) appear to be extracted from Sieper et al where the number of patients in both arms are inconsistent from the former source."	Please update text to "However, baseline BASDAI and the corresponding standard deviation (SD) were extracted from Sieper et al since they were not available in the TA497 committee papers" Please also update the reference to: Sieper et al, 2015 (A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active non-radiographic axial spondyloarthritis)	The current statement is misleading as it implies that available data were overlooked. Rather, the data were not available in TA497, so another source was used. The currently provided reference is for a different trial with a different intervention.	Not a factual inaccuracy, but the ERG has amended the statement to: "However, baseline BASDAI and the corresponding standard deviation (SD) appear to be extracted from Sieper *et al*[22], since they were not available in the TA497 committee papers. The ERG noted that the patient population is different in the two sources." The correct reference has been added to the report.

Issue 23 Clarity of graphs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 74 No legends are provided for Figure 10.	Add legends to Figure 10.	It is not currently possible to interpret the graphs in Figure 10. Whilst Novartis recognises that this is not a factual inaccuracy on the part of the ERG, nevertheless, we are unclear on how to interpret the graph, and some further detail would be extremely helpful.	The ERG has corrected the legends in Figure 10 and added further interpretation of the graph in the ERG report

Issue 24 Implementation of utility model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76 The ERG state "the ERG identified some minor programming errors relating to the signs and the coefficients used in the utility models in the CS"	Please clarify this statement or remove if no longer applicable.	The implementation of the York utility model in the CS includes a coefficient of +0.00788 for BASDAI; the ERG model includes an amended coefficient in which the sign is reversed (i.e. -0.00788). However, in both Corbett et al and the committee papers for TA383, the coefficient for BASDAI is consistent with the implementation presented in the CS.	The source that the company identified have misreported the coefficient on BASDAI. The ERG has access to the original model used in the TA 383 and can confirm that a coefficient of -0.00788 was used. Furthermore, it makes more clinical sense for the coefficient to be negative as it implies that increasing disease activity leads lower quality of life

Issue 25 Description of company sequencing scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63 The ERG states that "In evaluating the cost-effectiveness of 1st line use of secukinumab the company's model does not consider subsequent treatment with biologics"	Please change to: "In evaluating the cost-effectiveness of 1st line use of secukinumab the company's model considers subsequent treatment with biologics in a scenario analysis"	The current statement does not reflect the inclusion of a sequencing scenario analysis in the company submission.	The ERG has been amended and now reads "In evaluating the cost-effectiveness of 1st line use of secukinumab the company's model does not consider subsequent treatment with biologics in the base case"
Page 79 The ERG states that "The scenario analysis presented in the original submission compared secukinumab followed by TNF	Please change the text to "The scenario analysis presented in the original submission compared secukinumab followed by a basket of TNFα inhibitors with	This does not affect the results in the report but should be corrected for completeness and accuracy. The sequencing scenario doesn't	The ERG report has been changed according to the company's proposed amendment

with conventional care", which wrongly describes the comparator modelled in the sequencing scenario of the CS.	each TNFα inhibitor followed by a basket of all other options."	compare to a single comparator (CC), and the ERG's statement is therefore incorrect.	
Page 98 The ERG states that "the company does not include subsequent treatment in assessing the cost-effectiveness of 1st line use of secukinumab, which is not reflective of clinical practice."	Please clarify this statement by replacing with: "the company did not include subsequent treatment in assessing the cost-effectiveness of 1st line use of secukinumab in their base-case analysis, but provided this in a scenario analysis."	The current statement mischaracterises what was performed in the economic evidence submitted. The CS included a scenario analysis in which SEC->mixed basket of TNFα inhibitors was compared against TNF->mixed-basket of other treatments.	The ERG report has been amended and now reads "the company does not include subsequent treatments in assessing the cost-effectiveness of 1st line use of secukinumab in its base case, which is not reflective of clinical practice"

Issue 26 Accuracy of a response provided by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 81–82 The ERG states that "The CS did not consider the use of secukinumab beyond second-line therapy. The ERG requested, at clarification, that the company discussed the use of secukinumab after 2 or 3 previous TNFα inhibitors (clarification question B7), but the company did not provide such discussion." This suggests that an incomplete justification was provided by the company, without explicitly including the reasons provided in response to question B7.	Please change the underlined text to "…previous TNFα inhibitors (clarification question B7). Given the lack of data on secukinumab in 2nd and 3rd line, no further discussion was provided by the company."	A discussion on outcomes for secukinumab at 2nd or 3rd line did not seem appropriate given the lack of data in these populations.	Not a factual inaccuracy

Issue 27 Incorrect items referenced

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 87 The ERG state that "the ERG undertook further validation checks and identified the errors mentioned in items 8, 13, 22 and 23"	Please amend item numbers if appropriate.	Incorrect item numbers appear to be referenced.	The ERG has fixed the cross-referencing problems in the ERG report

Issue 28 Misreporting of base-case ICER

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 95 In Table 25, the reported CS base-case ICER (1st line use of SEC) should be [redacted], not [redacted].	Please correct.	The correct ICER was provided as part of the responses to the ERG clarification questions. This does not directly impact the interpretation of any results but should be corrected for accuracy.	The ERG has changed the ERG report according to the company's proposed amendments
Page 83 In the Table 20, the incremental costs and QALYs for adalimumab biosimilar are reported to be £8,181 and 1.49	Please correct these values to be [redacted] and [redacted]	This does not directly impact the interpretation of any results, but should be corrected for accuracy.	The ERG has changed the ERG report according to the company's proposed amendments

Issue 29 Error in the sequencing described in the ERG's base-case results table

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 97 In Table 27, the final column's header is "ICER (TNFi->SEC->CC vs TNFi->TNFi->CC)", and the ICERs reported are labelled with "(for TNFi)". This labelling is not clear, as the ICERs reported are for TNFi->TNFi->CC vs TNFi->SEC->CC.	Please either: • Change the table heading to "TNFi->TNFi->CC vs TNFi->SEC->CC", or • Label each reported ICER with "(for TNFi->TNFi->CC)" instead of "(for TNFi)".	This has no impact on model results but should be relabelled for accuracy and clarity of interpretation of the ICERs reported.	The ERG has changed the column name in Table 27 to read "TNFi->TNFi->CC vs TNFi->SEC->CC" and the label of each reported ICER to read "(for TNFi sequence)"

Confidentiality marking

Issue 30 Acquisition cost of secukinumab confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 77 In "Table 16: Drug acquisition costs", the first row (Secukinumab) is marked up as academic in confidence, but should be marked as commercial in confidence, instead.	Please change the marking to commercial in confidence.	This should be correctly marked up for accuracy. The cost of secukinumab including the PAS is commercial in confidence.	The ERG has changed the ERG report according to the company's proposed amendment

Issue 31 Market share information confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 78 The market share information reported in Table 17: Market share information should be marked up as commercial in confidence.	Please mark-up this table.	This should be marked up to ensure commercially sensitive information remains confidential.	The ERG has changed the ERG report according to the company's proposed amendment

Issue 32 Cost-effectiveness plane and frontier confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84	Please mark-up this figure as commercial in confidence.	This should be marked up to ensure commercially sensitive	The ERG has changed the ERG report according to the

The cost-effectiveness plane and frontier shown in “Figure 13: Cost-effectiveness plane and efficiency frontier for 1st line use of secukinumab in the CS” should be marked as commercial in confidence.		information relating to the PAS for secukinumab remains confidential.	company’s proposed amendment

Issue 33 Description of results confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 85 The following text should be marked up as commercial in confidence: [redacted]	Please mark-up this text as commercial in confidence.	This should be marked up to ensure commercially sensitive information relating to the PAS for secukinumab remains confidential.	The ERG has amended the CiC marking in the ERG report in the following manner which ensures that commercially sensitive information relating to the PAS for secukinumab remains confidential “The results of both analyses highlight that, in first line, secukinumab is [redacted] and considerably less effective (dominated) than adalimumab (biosimilar), the cheapest TNFα inhibitor available.”

Issue 34 Reporting of results confidentiality marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 85	Please mark-up the entire table as commercial in confidence.	This should be marked up to ensure commercially sensitive	The ERG has changed the ERG report according to the

“Table 21: Full incremental analysis of 1st line use of secukinumab compared to a single TNFα-inhibitor (combined load and no-load arms)” is only partially marked up as commercial in confidence.		information relating to the PAS for secukinumab remains confidential.	company’s proposed amendment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Secukinumab for treating non-radiographic axial spondyloarthritis

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Disease background: non-radiographic axial spondyloarthritis

- Axial spondyloarthritis (axSpA) is a chronic rheumatic condition, characterised by inflammation at the sacroiliac joint and spine. AxSpA is an umbrella term encompassing both non-radiographic axial spondyloarthritis (nr-axSpA) and radiographic axial spondyloarthritis (rad-axSpA, also known as ankylosing spondylitis).

- Nr-axSpA differs from rad-axSpA/ankylosing spondylitis by the absence of visible structural damage on plain X-rays in the sacroiliac joints or spine. Inflammation may be visible on an MRI (magnetic resonance imaging) scan. The advent of MRI was important as it enabled earlier detection, therefore earlier treatment, of axSpA, since joint damage may not become evident on radiography for many years.

- The underlying mechanisms of disease are thought to be autoimmune and autoinflammatory, with the major mediators being the pro-inflammatory cytokines tumour necrosis factor (TNF)-alpha and interleukin (IL)-17A. Genetics plays a role in the development of nr-axSpA, especially the human leucocyte antigen (HLA)-B27 allele, though its presence is not essential.

- Common symptoms associated with nr-axSpA include chronic back pain, stiffness, fatigue, poor sleep quality and night-time waking. Joint and tendon pain, stiffness, fatigue, arthritis and swelling of the fingers are also common, resulting in significantly reduced physical function. Extra-articular symptoms such as psoriasis, inflammatory bowel disease and inflammation of the eye occur in a substantial proportion of people. The burden of disease (in terms of functionality and self-reported disease activity) and effect on quality of life are similar between nr-axSpA and rad-axSpA/ankylosing spondylitis.

- Prevalence data are sparse due to disease heterogeneity, slow progression and delay in diagnosis but estimates range from around 0.1–0.4% in the general population. AxSpA affects approximately equal proportions of men and women, however nr-axSpA is more prevalent in women.

- The Assessment of SpondyloArthritis International (ASAS) Society criteria uses imaging or clinical arms to classify axSpA. All patients must have developed chronic back pain (of at least 3 months duration) before 45 years:

    - The **imaging** arm of the ASAS criteria requires evidence of joint damage (erosions or fusion) due to sacroiliitis using either radiography (rad-axSpA classification) or MRI (nr-axSpA classification). In addition to this, at least one of the following spondyloarthritis features is also required: inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's/colitis, good response to non-steroidal anti-inflammatory drugs (NSAIDs), family history of spondyloarthritis, HLA-B27 genetic marker, or elevated C-reactive protein (CRP).
    - The **clinical** arm of the criteria requires that patients must test positive for the HLA-B27 genetic marker and also have at least two spondyloarthritis features above to be classified as nr-axSpA

1.2 Treatment pathway

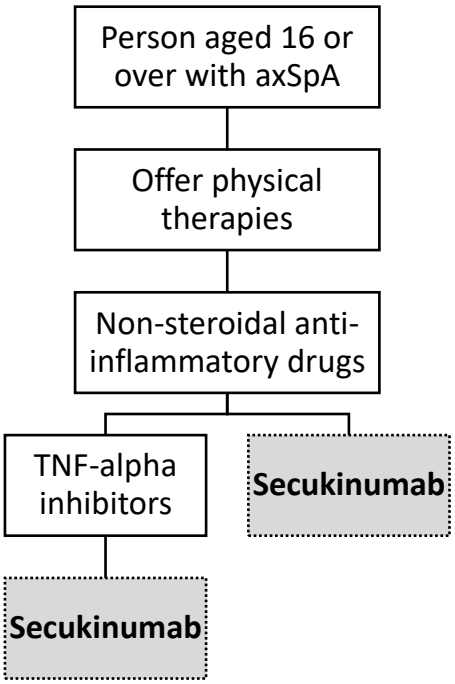
- There is no cure for nr-axSpA. Treatment aims to relieve pain and stiffness, prevent joint and organ damage, preserve joint function,mobility and delay progression to rad-axSpA.

- NICE guideline 65 recommends conventional treatment with physical therapies initially and first line pharmacological treatment with non-steroidal anti-inflammatory drugs (NSAIDs) for treating nr-axSpA.

- For patients who respond inadequately or cannot tolerate NSAIDs, technology appraisals 383 and 497 recommend TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab) as options for treating severe nr-axSpa. Treatment with a TNF-alpha inhibitor should only be continued if there is clear evidence of response after 12 weeks, defined as a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value, or by 2 or more units, OR a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more.

- Technology appraisal 383 recommends treatment with another TNF-alpha inhibitor for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response.

Treatment pathway for managing spondyloarthritis and proposed positioning of secukinumab



1.3 Secukinumab

Marketing authorisation	Treatment of active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs)
Mechanism of action	Monoclonal antibody that binds to and neutralises the activity of the proinflammatory cytokine IL-17A
Administration and dose	Subcutaneous injection with a pen or pre-filled syringe. The recommended dose is 150 mg administered subcutaneously at Weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing.
List price	£1,218.78 for 2 x 150 mg Annual cost of treatment First year: £9,750.24 Subsequent years: £7,312.68 A confidential discount on the price has been agreed.

1.4 Decision problem

	NICE scope	**Company's decision problem**	**Rationale if different**
Population	People with nr-axSpA with objective signs of inflammation, whose disease has responded inadequately to, or who are intolerant to, NSAIDs	As per scope	N/A
Intervention	Secukinumab	As per scope	N/A
Comparators	• Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Established clinical management without biological treatments	As per scope	N/A

	NICE scope	Company's decision problem	Rationale if different
Outcomes	• Disease activity • Functional capacity • Disease progression • Pain • Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • Symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • Adverse effects of treatment • Health-related quality of life	As per scope, except for peripheral arthritis, dactylitis, and symptoms of extra-articular manifestations.	The outcomes not included were not measured outcomes in the PREVENT trial
Subgroups	If evidence allows, subgroups of people who have, had or not had, prior exposure to biological therapy.	As per scope	Only secukinumab and certolizumab pegol trials included a small proportion of patients who have had prior exposure to a biological therapy.

1.5 Clinical evidence

- The primary source of clinical effectiveness evidence was the PREVENT trial

Study design	Phase III, double-blind, randomised, multicentre
Location	International: 140 sites in 24 countries; 9 sites in UK (24 randomised patients)
Population	Adults fulfilling the ASAS classification criteria for axSpA plus an abnormal CRP and/or MRI, with no radiographic evidence of changes in the sacroiliac joints that would meet the modified New York criteria for rad-axSpA (**n=555**)
Intervention(s)	Secukinumab (with load dose) (**n=185**) Secukinumab (without load dose) (**n=184**)
Comparator(s)	Placebo (**n=186**)
Outcomes	**Primary outcome:** • Proportion of TNF-alpha-inhibitor-naïve patients achieving an ASAS40 response at Week 16 (disease activity) **Secondary outcomes:** • Disease activity • Functional capacity • Adverse effects of treatment • Health related quality of life

1.6 Descriptions of study assessment

Assessment	Description
Efficacy assessments	
Assessment of SpondyloArthritis International Society criteria (ASAS)	Main ASAS domains: 1. Patient's global assessment of disease activity measured on a VAS 2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS 3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS 4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS Additional assessment domains: 5. Spinal mobility represented by the BASMI lateral spinal flexion assessment 6. C-reactive protein (acute phase reactant)
ASAS Response Criteria-20% (ASAS20)	Improvement of ≥20% and ≥1 unit on a scale of 10 in at least 3 of the 4 main domains and no worsening of ≥20% and ≥1 unit on a scale of 10 in the remaining domain
ASAS Response Criteria-40% (ASAS40)	Improvement of ≥40% and ≥2 units on a scale of 10 in at least 3 of the 4 main domains and no worsening at all in the remaining domain
ASAS 5/6 improvement criteria	Improvement of ≥20% in at least 5 of all 6 domains
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	6 questions (0–10 scale on a VAS) pertaining to the 5 major symptoms of axSpA: fatigue, spinal pain, joint pain /swelling, areas of localised tenderness (called enthesitis, or inflammation of tendons and ligaments), morning stiffness duration, morning stiffness severity
BASDAI50	The BASDAI50 was defined as an improvement of at least 50% in the BASDAI compared with baseline
Bath Ankylosing Spondylitis Functional Index (BASFI)	10 questions (0–10 scale on a VAS) designed to determine the degree of functional limitation in those patients with rad-axSpA. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patients' ability to cope with everyday life (65, 66)
Patient's assessment of back pain intensity (VAS)	Assessed using a 100 mm VAS ranging from no pain to unbearable pain, after the question "Based on your assessment, please indicate what is the amount of back pain at any time that you experienced during the last week?" and "Based on your assessment, please indicate what is the amount of back pain at night that you experienced during the last week?"

Assessment	Description
Quality of life assessments	
Medical Outcome Short Form Health Survey (SF-36) Version 2 (Acute Form)	SF-36 is a widely used and extensively studied instrument to measure HRQoL among healthy patients and patients with acute and chronic conditions. It consists of 8 subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health.
Ankylosing Spondylitis Quality of Life (ASQoL)	Self-administered questionnaire designed to assess HRQoL in adult patients with rad-axSpA. The ASQoL contains 18 items with a dichotomous yes/no response option. A single point is assigned for each "yes" response and no points for each "no" response resulting in overall scores that range from 0 (least severity) to 18 (highest severity).
Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue©)	The FACIT-Fatigue© is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. The purpose of FACIT-Fatigue in this study was to assess the impact of fatigue on patients with nr-axSpA.
EuroQol 5D	The EQ-5D is a widely used, self-administered questionnaire designed to assess health status in adults.

1.7 Key trial results

- The primary source of clinical effectiveness evidence was the PREVENT trial

Primary endpoint: ASAS40 response in TNF-alpha-ihibitor-naïve patients using non-responder imputation at week 16; full analysis set (FAS)

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=164)	68/164 (41.5)	vs No Load	0.98	[redacted]	[redacted]
		vs placebo	1.72	[redacted]	0.0197
Secukinumab 150 mg No Load (N=166)	70/166 (42.2)	vs placebo	1.76	[redacted]	[redacted]
Placebo (N=171)	50/171 (29.2)	N/A			

Source: Table 14, company submission (page 54)

Secondary endpoint: ASAS40 response in all patients using non-**responder imputation at week 16; FAS**

Treatment group	n/M (%)	Comparison	OR	95% CI	p-value
Secukinumab 150 mg Load (N=185)	74/185 (40.0)	vs No Load	0.98	[redacted]	[redacted]
		vs placebo	1.77	[redacted]	[redacted]
Secukinumab 150 mg No Load (N=184)	75/184 (40.8)	vs placebo	1.80	[redacted]	[redacted]
Placebo (N=186)	52/186 (28.0)	N/A			

Source: Table 16, company submission (page 56)

- The ERG summarised the odds ratios or mean difference between secukinumab with load arm compared with placebo in all patients for the main outcomes reported in the company submission below. Results show that [redacted].

Outcome	Odds ratio (OR) or mean difference (MD)	95% Confidence interval
ASAS40	OR 1.77	[redacted]
ASAS 5/6	OR [redacted]	[redacted]
BASDAI	MD [redacted]	[redacted]
BASDAI50	OR [redacted]	[redacted]
BASFI	MD [redacted]	[redacted]
SF36 PCS*	MD [redacted]	[redacted]
SF36 MCS*	MD [redacted]	[redacted]
ASQoL	MD [redacted]	[redacted]
FACIT-fatigue	MD [redacted]	[redacted]
EQ-5D	MD [redacted]	[redacted]

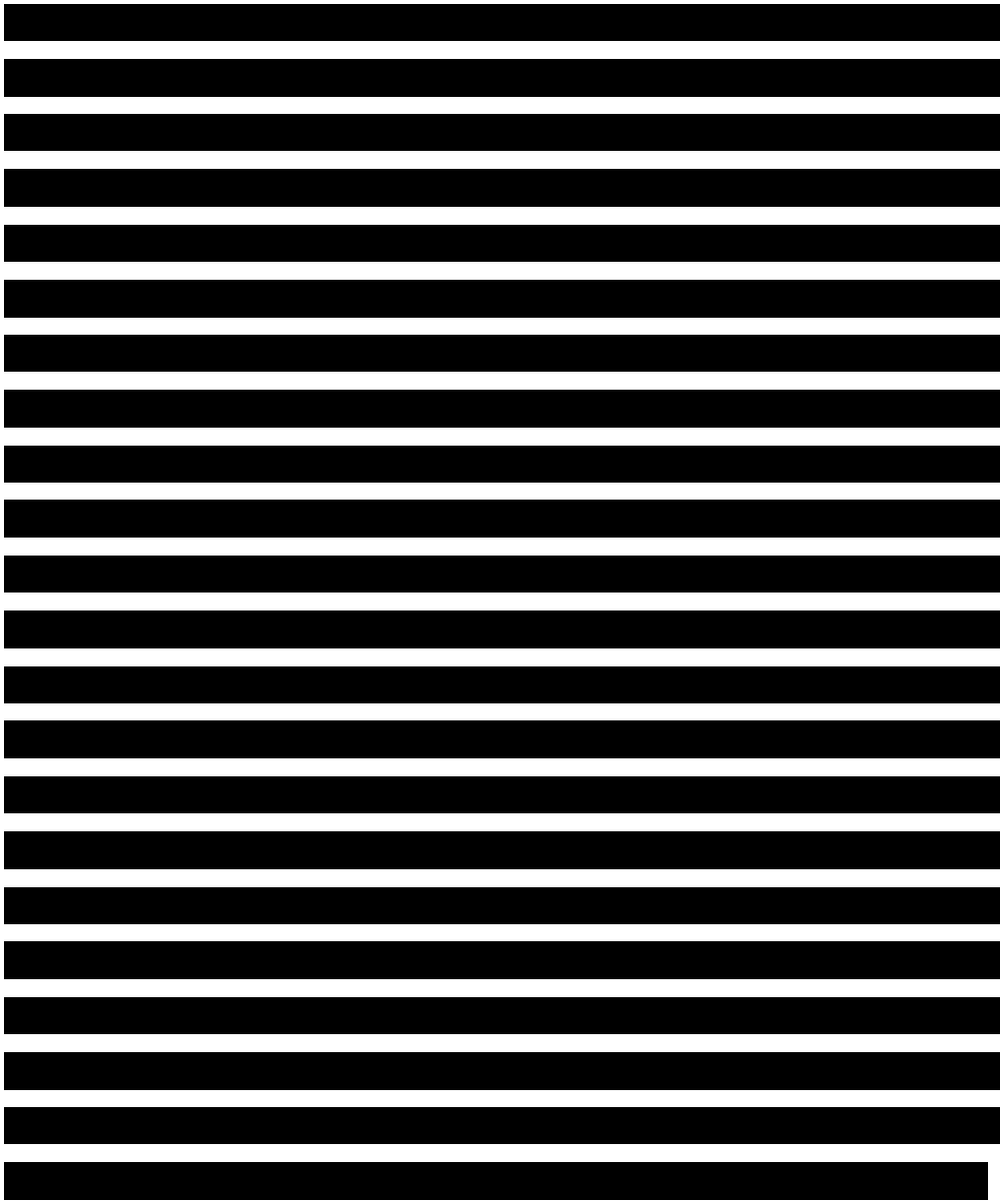
Source: Table 3, ERG report (page 28)
*PCS: physical component summary MCS: mental component summary

- Results for both secukinumab arms with and without load dose were [redacted]. The difference between load and no-load arms in the

[redacted] and was [redacted] Therefore, whether [redacted]

1.8 Key subgroups

- PREVENT included a subgroup of [redacted]. Relative effect estimates versus placebo were [redacted]. For the [redacted].
- Enrolment in PREVENT ensured that no less than 15% of patients were to belong to either of the three subgroups of "objective signs of inflammation":
    - patients with both evidence of sacroiliitis on MRI imaging and elevated (>5 mg/l) CRP levels (MRI+/CRP+) **(n=151**)
    - patients positive for MRI imaging but negative for elevated CRP levels (MRI+/CRP-) (**n=345**)
    - and patients negative for MRI imaging and positive for elevated CRP levels (MRI-/CRP+) (**n=216**)
- Subgroup analysis suggested that [redacted] This appears to be because [redacted].

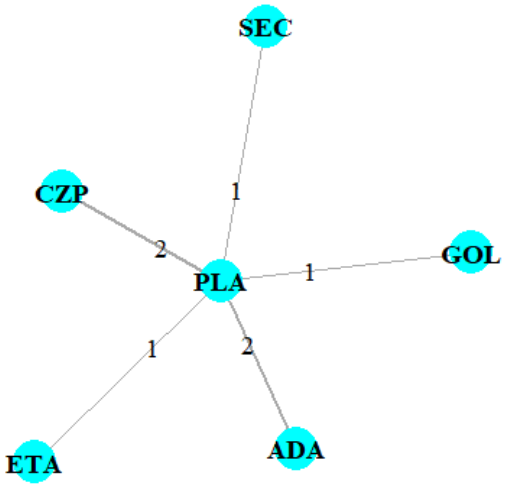


1.9 **Network meta-analyses (NMAs)**

- The company conducted an NMA to compare the relative efficacy of secukinumab compared to TNF-alpha inhibitors (etanercept, adalimumab, golimumab, and certolizumab pegol). None of the active treatments are compared directly in trials, therefore the common placebo comparator was used to form a (star shaped) network connecting all treatments. The company's base-case NMA included data from 7 RCTs at 16 weeks and included outcome data for (i) ASAS40, (ii) BASDAI50, (iii) BASDAI change from baseline (CFB), and

(iv) BASFI CFB as these outcomes were included in the economic model.

Diagram for the overall network



The numbers on the lines represent the number of trials comparing the two connected treatments. ADA=adalimumab, CZP= certolizumab pegol, ETA= etanercept, GOL=golimumab, PLA= placebo and SEC= secukinumab.

- The base case NMA incorporated in the economic modelling was based on the joint modelling approach used in TA383. In this model, responses on BASDAI50 and BASDAI change from baseline were related to each other and BASDAI and BASFI change from baselines were assumed to be correlated. All TNF-alpha inhibitors were assumed to have an exchangeable treatment effect, that is, the treatment effects are similar but not identical. Inferences about the effectiveness of each TNF-alpha inhibitor borrow strength across the treatment class, shrinking the estimates towards the mean of the class effect and these shrunken estimates are used in the economic model. Only fixed effects models were fitted, that is between-study heterogeneity was not considered in the joint modelling.

- The ERG re-conducted the NMA by using data from the pooled load and no-load arms of secukinumab and included the results in its base-case analysis.

1.10 **NMA results**

- Biologics (TNF-alpha inhibitor treatments as well as secukinumab) showed [redacted]

- The company considers that secukinumab [redacted]. The ERG notes that although confidence intervals are wide for each treatment, each analysis approach produces a [redacted]

- The company considers that [redacted] results and highlights that there may be several reasons why the treatment effect of secukinumab [redacted]

NMA results of secukinumab compared to other treatments

		BASDAI50 Response	BASDAI CFB	BASFI CFB
		Odds Ratio	Mean Difference	Mean Difference
Adalimumab	Median	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	95% CrI	[redacted]	[redacted]	[redacted]
Certolizumab pegol	Median	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	95% CrI	[redacted]	[redacted]	[redacted]
Etanercept	Median	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	95% CrI	[redacted]	[redacted]	[redacted]
Golimumab	Median	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	95% CrI	[redacted]	[redacted]	[redacted]
TNF-alpha Inhibitors (Class)	Median	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	95% CrI	[redacted]	[redacted]	[redacted]
Conventional Care	Median	[redacted]	[redacted]	[redacted]
	Mean	[redacted]	[redacted]	[redacted]
	95% CrI	[redacted]	[redacted]	[redacted]

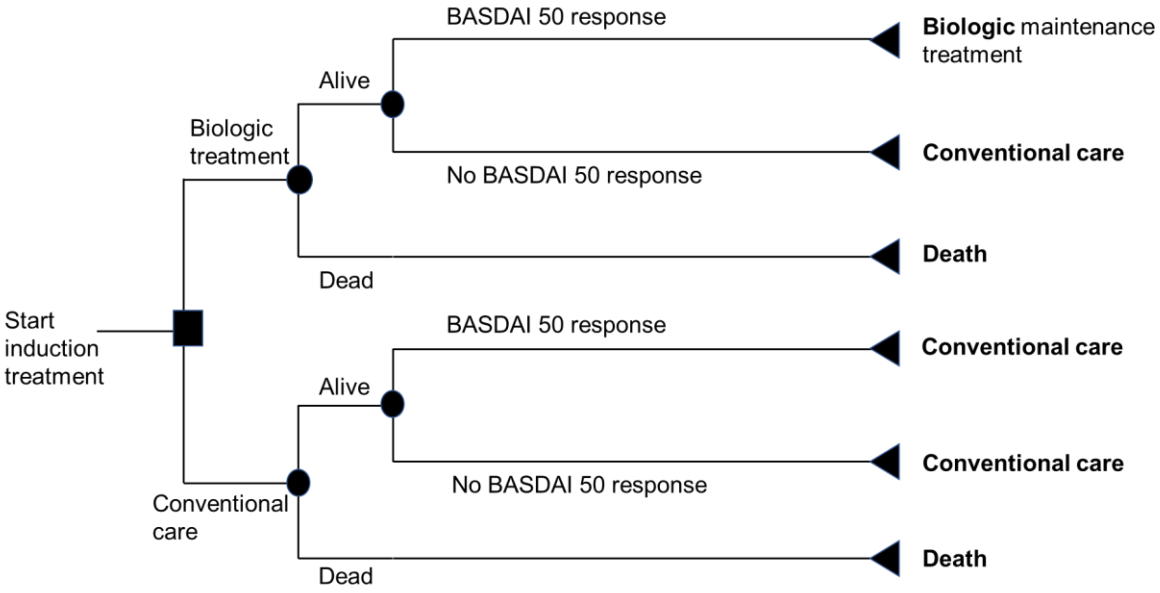
Source: Table 11, ERG report (page 50-51)

1.11 Model structure

- The economic model is structured as a short-term decision tree (induction period) followed by a long-term Markov model. In the induction period, patients enter the model and receive three months of induction treatment (given that a 12-week stopping rule is applied for TNF-alpha inhibitors and a 16-week stopping rule is applied for secukinumab). At the end of this induction period, patients are assessed for BASDAI50 response and enter the Markov model. Those who do not achieve a BASDAI50 response (non-responders) discontinue their initial treatment. Those who achieve a BASDAI50 response (responders) continue with the same biologic therapy. Most

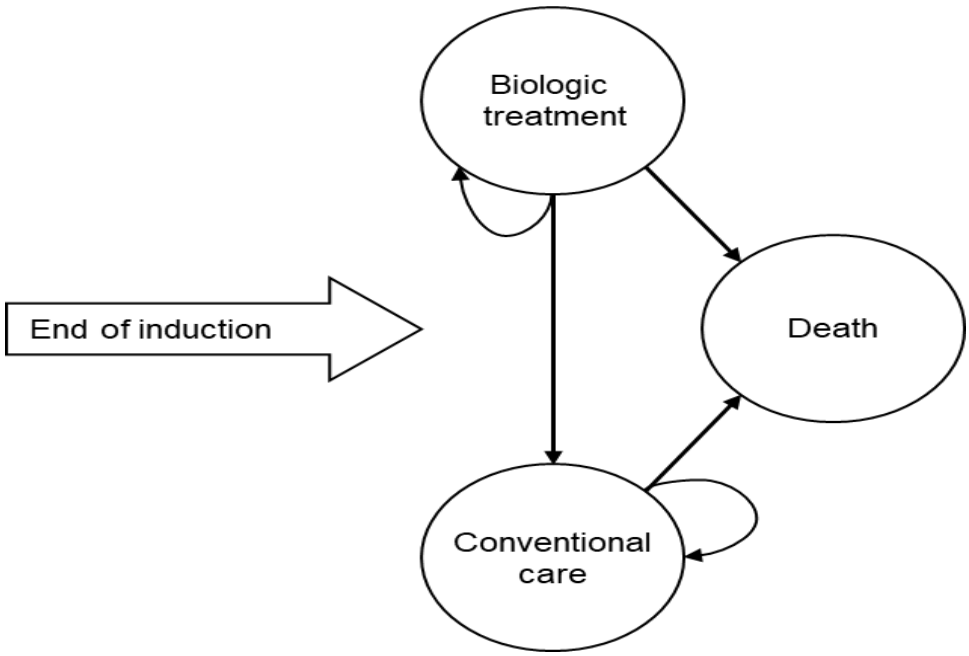
model parameters (excluding relative effectiveness parameters) were assumed equal to those in the model considered for TA383.

Structure of decision-tree covering the initial period until BASDAI50 response assessment.



Source: Figure 7, ERG report (page 64)

Post-induction Markov model structure.



Source: Figure 8, ERG report (page 65)

1.12 Key model assumptions

Population characteristics	Patients with nr-axSpA (defined by the 2009 ASAS classification criteria) with objective signs of inflammation (MRI+ and/or CRP+), who were intolerant or whose disease has responded inadequately to treatment with ≥ 2 NSAIDS as described in PREVENT. Two patient groups considered seperately: 1) biologic-naïve (primary or base case analysis) and biologic-experienced patients (secondary analysis, i.e. patients who have received one previous TNF-alpha inhibitor, as per PREVENT).
Intervention	150mg of secukinumab with loading dose administered at weeks 0,1,2,3,4 followed by one dose every month
Comparator	In the base case analysis (biologic-naïve group), secukinimab was compared with conventional care (NSAIDS and physiotherapy) and TNF-alpha inhibitors currently licenced for nr-axSpA (adalimumab, certolizumab pegol, etanercept and golimumab). In the secondary analysis (biologic-experienced patients), the comparator was conventional care.
Treatment effectiveness	In the base-case that considers treatment naïve patients,treatment specific response to BASDAI50 and changes in BASDAI and BASFI after induction (e. at 12-weeks for TNF-alpha inhibitors and at 16-weeks for secukinumab) informed by NMA.
Adverse events	Only adverse events considered are non-melanoma skin cancer and serious infections.
Utilities	Base case utilities taken from EQ-5D-5L data mapped to 3L valuation set from PREVENT
Time horizon	Lifetime (100 years)
Perspective	NHS and Personal Social Sevices
Discount rates	3.5% for costs and outcomes
Costs	Drug acquisition, administration, monitoring, disease management and adverse events costs. Sourced from NHS reference costs, PSSRU, BNF and eMIT.

2. Summary of the technical report

2.1 In summary, the technical team considered the following:

Issue 1 It is important to understand if clinicians would use secukinumab first-line in preference to TNF-alpha inhibitors or if secukinumab would mostly be used after TNF-alpha inhibitors had failed or if TNF-alpha inhibitors were contraindicated. The population in PREVENT may not reflect the population for whom secukinumab will be used in clinical practice as it included a biologic naïve population that had not been treated with TNF-alpha inhibitors previously. It is also important to determine the clinical need for a new treatment, current use of TNF-alpha inhibitors and the population likely to benefit most from treatment with secukinumab.

Issue 2 Higher baseline BASFI scores in PREVENT may mean that trial results are not generalisable to clinical practice as baseline BASFI scores are expected to be lower in people receiving first-line treatment for nr-axSpA. Higher baseline BASFI scores may also adversely affect results for secukinumab because a lower BASFI is considered to be a good predictor of response.

Issue 3 The response criteria to determine continuation of treatment in PREVENT beyond 12 weeks are different from the composite criteria in the NHS. It is not clear how many patients in the PREVENT trial would fulfil the response criteria used in the NHS and this raises concerns about whether the long term clinical effectiveness estimates from PREVENT are appropriate and can be used in the economic analyses to generate cost effectiveness estimates for an NHS population.

Issue 4 The company considered results for secukinumab with the load dose only in its analyses. Due to the similarity in outcomes

between the load and no-load arms, it is appropriate to pool the results from both arms to inform the effectiveness of secukinumab and reduce the uncertainty around the results.

Issue 5 It is important to establish whether there are any groups of people for whom secukinumab would be more or less clinically and cost effective than the overall population in clinical practice. Subgroup analyses from PREVENT suggest that secukinumab may be more effective in certain subgroups, however the PREVENT trial was not powered to detect differences between subgroups therfore it is not possible to conclude that there is genuine heterogeneity in treatment effect.

Issue 6 It is important to determine if secukinumab is expected to have poorer treatment effects compared to most TNF-alpha inhibitors in clinical practice as suggested by results from the NMA and if the potential underestimation of the effect estimates for secukinumab in the NMA can be explained.

Issue 7 The company's base case model assumes that baseline BASDAI and BASFI scores are conditional on response. The ERG's also assumes conditional baselines in its base-case but notes that whether baselines should be conditional on response is an area of uncertainty and changing to a common baseline model significantly impacts cost-effectiveness estimates and favours TNF-alpha inhibitors.

Issue 8 Costs for TNF-alpha inhibitors are the key driver of cost effectiveness analyses. In line with TA383, the least expensive nationally available TNF-alpha inhibitor (taking into account administration costs and patient access schemes) should be used to represent the class at first line. This should be the cost of the adalimumab biosimilar , the cheapest TNF-alpha inhibitor

available.The company's results for first-line use indicate that secukinumab is slightly more costly and considerably less effective (dominated) than the adalimumab biosimilar. Exploratory analyses of secukinumab second line also show that secukinumab is only cost-effective if second-line TNF-alpha inhibitors are costed using the company's market share data rather than biosimilars.

Issue 9 The company's base case model has not been implemented correctly as it does not consider subsequent treatment in assessing the cost-effectiveness of first line use of secukinumab, which is not reflective of clinical practice. Subsequent treatment with biologics should be considered to establish the cost-effectiveness of first-line use of secukinumab as NICE recommends sequential use of TNFs (TA383) and hence these are relevant comparators when secukinumab is positioned as a second-line therapy.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- There is inadequate evidence for second-line use of secukinumab from PREVENT as the company's analyses of biologic-experienced patients is based on a very small subgroup from PREVENT.

- Although the network meta-analyses (NMA) methodology was considered to be appropriate, there is considerable uncertainty about the effectiveness of secukinumab compared to TNF-alpha inhibitors for people with nr-axSpA.

- It remains uncertain whether baseline BASDAI and BASFI should be conditional on response. The impact of this on cost-effectiveness in a model where subsequent treatments are considered is also unknown. Whilst conditional baselines have been justified on the basis of the use

of the relative BASDAI50 criteria, the composite response criteria used in clinical practice is likely to diminish such an effect.

- The company, did not use recently published data to extend the long-term BASFI changes based on the rate of conversion from nr-axSpA to rad-axSpA. This means that the long-term BASFI progression may be overestimated in the company's model.

- The company assumes the effect of secukinumab on BASFI progression to be equal to that of TNF-alpha-inhibitors. The ERG noted that PREVENT offered no evidence of such an effect for secukinumab. Therefore, there is uncertainty over the treatment effect modification of long-term progression.

2.3 The cost-effectiveness results include a confidential discount on the price for secukinumab.

2.4 No equality issues were identified.

3. Key issues for consideration

Issue 1 – Place of secukinumab in the treatment pathway

Background/description of issue	PREVENT included a subgroup of [redacted]. Relative effect estimates versus placebo were [redacted]. The **ERG's** clinical adviser noted that a higher proportion of patients will have received another biologic before using secukinumab in clinical practice and it was unlikely that secukinumab would be used as a first-line biologic therapy for most patients. He considered that secukinumab would mostly be used either as a second-line biologic (in patients who did not respond at all to their first TNF-alpha inhibitor) or as a last-line biologic (in patients who had some response to TNF-alpha inhibitors). The **ERG** noted that the proportion of patients in PREVENT who have previously been treated with a biologic ([redacted]) may not be reflective of the population in the NHS that would receive secukinumab and that the proportion of people having received previous treatment with a TNF-alpha inhibitor is likely to be much higher. This raises concerns about the generalisability of trial results to clinical practice in the NHS. The proposed MA does not limit the use of secukinumab to a particular line of treatment, hence it could be considered at first- line, at second- or third-line (where patients may still be considered for TNF inhibitors) and after failing TNF treatment. The company presents evidence mainly for first-line use of secukinumab (in line with the available efficacy evidence), but also submits an analysis at second-line based on the small subgroup outlined above, which the ERG deems not to be robust for decision making purposes. No evidence has been submitted on end of line use of secukinumab.
Why this issue is important	It is important to establish where secukinumab would be used in the treatment pathway. More than [redacted] of the people who would have secukinumab in clinical practice may have had previous treatment with a TNF-alpha inhibitor and therefore the PREVENT results may not be generalisable to clinical practice.

Questions for engagement	a. Is the proportion of patients in PREVENT treated with secukinumab who have previously had a TNF-alpha inhibitor (■) reflective of the population in the NHS that would receive secukinumab? b. Where is secukinumab most likely to be used in the treatment pathway? ○ Would secukinumab be used as a first-line biologic for treating nr-axSpA in clinical practice? ○ Would secukinumab be a treatment option for people when TNF-alpha inhibitors have proven to be ineffective or are not tolerated? ○ Would secukinumab be considered an alternative treatment option to TNF-alpha inhibitors in a first-line setting or is it more likely to be considered an option after treatment with TNF-alpha inhibitors has failed or is contraindicated? ○ Is there a clinical need for seckinumab based on current clinical practice? What target population is likely to benefit most from treatment with secukinumab? c. Are the trial results from the first line setting generalisable to second line use?
Technical team preliminary judgement and rationale	The proposed marketing authorisation does not limit the use of secukinumab to a particular line of treatment. However, clinical advice so far suggests that secukinumab would mostly be used after TNF-alpha inhibitors and not as a first-line treatment. Therefore, the population in PREVENT may not reflect the population for whom it will be used in clinical practice. It is also important to determine the clinical need for a new treatment and the patient population likely to benefit most from treatment with secukinumab.

Issue 2 –High baseline BASFI in PREVENT trial population

Background/description of issue	Baseline demographics and disease characteristics were generally well balanced across treatment groups in PREVENT. Mean age was 39.4 years, mean body mass index (BMI) was [redacted] kg/m^2, and there were more female (54.1%) than male (45.9%) patients. Overall, patients had a mean time since onset of back pain of 8.56 years and a mean time since first diagnosis of axSpA of [redacted] years. [redacted]. The majority of patients (90.3%) were naïve to TNF-alpha inhibitors, and 9.7% of patients had received one prior TNF-alpha inhibitor with inadequate response or intolerance. BASFI, BASDAI and BASMI characteristics at baseline were similar across treatment groups, with an overall mean BASFI score of [redacted], a mean BASDAI score of [redacted] and a mean BASMI (linear) score of [redacted] The **ERG's** clinical adviser considered that the baseline characteristics were reasonably representative of the patient population likely to receive a biologic in the NHS. However, the baseline BASFI scores (around 6) were higher than what would be expected in clinical practice and indicate a high functional impairment in the sample recruited. Data from 12 registries in the EuroSpA collaboration indicate a median BASFI of around 5 is more representative and populations in the other clinical trials of TNF-alpha inhibitors in nr-axSpA patients have mean BASFIs of around 5 to 5.5. The **ERG** therefore considers that BASFI baseline values in the EuroSpA registry are likely to better reflect first-line nr-axSpA patients and it used these when it updated the company's cost effectiveness analysis.
Why this issue is important	High baseline BASFI scores may mean that the trial results are not generalisable to clinical practice. In addition, the company considered that the high baseline BASFI scores would adversely affect the results for secukinumab because lower BASFI is considered to be good predictor of response. However, the **ERG** notes that the evidence for a lower BASFI score being indicative of a good response relates to patients with rad-axSpA and it did not believe that there was convincing evidence for this in people with nr-axSpA.
Questions for engagement	a. Is a population with an overall mean BASFI value of 6 representative of the those seen in the NHS? b. Is the higher overall mean baseline BASFI value of 6 in PREVENT likely to adversely affect the trial and NMA results for secukinumab? c. Are baseline BASFI values from the EuroSpA registry more representative of clinical practice in the UK?

Technical team preliminary judgement and rationale	A high baseline BASFI score of 6 (indicating higher functional impairment) in the trial population may mean that the results are not generalisable to clinical practice as baseline BASFI scores are expected to be lower in people receiving first-line biologic treatment for nr-axSpA. Higher baseline BASFI scores could result in an underestimate of response to secukinumab because lower BASFI is considered to be good predictor of response in rad-axSpa and this might apply to nr-axSpa.

Issue 3– Continuation of treatment criteria in PREVENT and longer-term clinical effectiveness

Background/description of issue	The **company** analysed long term clinical effectiveness data for TNF-alpha inhibitors naïve patients up to 52 weeks in PREVENT. The results may have limited relevance to the NHS due to the continuation/stopping rules used. 'Inadequate response' was not formally defined but was instead decided following discussion between clinician and patient. Clinical experts stated that BASDAI and VAS spinal pain criteria would be used in the NHS. NICE guideline 65 recommends that treatment with adalimumab, certolizumab pegol, and etanercept should only be continued if there is clear evidence of response after 12 weeks, defined as: • a reduction in the BASDAI score to 50% of the pre-treatment value, or by 2 or more units, and • a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more The proposed induction period for secukinumab (16 weeks) differs from the 12 week period for TNF-alpha inhibitors. In the appraisal of secukinumab for rad-axSpA (TA 407), the committee concluded that the 16-week assessment of response was in line with the marketing authorisation and was hence acceptable for decision making. In PREVENT, open label 'escape treatment' of secukinumab was available for all patients who did not respond at 20 weeks. Non responders were classified by lack of 'response' to secukinumab based on "the clinical judgement of disease activity by the investigator and the patient to reflect the real-world setting". Therefore, no response criteria were pre-specified for the escape treatment. It is unclear how many patients in the PREVENT trial would fulfil these response criteria for continuation of treatment and this raises concerns about the generalisability of the trial results to clinical practice. The **ERG** identified data in a recent paper of a UK cohort of patients with axial spondyloarthritis (mostly patients with rad-axSpA, but some with nr-AxSpA) which indicated that a BASDAI50 response and/or a 2 or more points reduction was achieved by 409/508 (81%) patients, whereas a BASDAI50 response was only achieved by 275 (54%). Response rates in rad-axSpA are generally higher than for nr-axSpA, but these data imply that the proportion of patients who may continue on a biologic is higher in clinical practice than is indicated solely by BASDAI50 results.

	In the company's base case model, response was based on patients' BASDAI50 status at the end of the induction period (12 weeks for TNF-alpha inhibitors and 16 weeks for secukinumab). This is in line with the approache taken in TA383. However,the composite criteria outlined above used in clinical practice significantly increases the proportion of responders. The company provides a sensitivity analysis using ASAS40 as a response criterion. Response to ASAS40 is of a similar level to BASDAI50 and does not significantly affect cost-effectiveness.
Why this issue is important	Longer term clinical effectiveness results may have limited relevance to a NHS population due to the continuation/stopping rules used. The response criteria to determine continuation of treatment in PREVENT beyond 12 weeks are different from the composite criteria in the NHS. It is not clear how many patients in the PREVENT trial would fulfil the response criteria used in the NHS and this raises concerns about whether the long term clinical effectiveness estimates from PREVENT are reliable and can be used in the economic analyses to generate cost effectiveness estimates for an NHS population.
Questions for engagement	a. Most patients in the trial continued treatment with secukinumab after 16 weeks. How does this impact interpretation of trial results given that continuation of treatment with secukinumab in clinical practice might be assessed on a different definition of 'response'? b. Will the use of a different composite response criteria in clinical practice to that used in the PREVENT trial result in more patients as being classed as 'non-responders'? c. The long-term clinical effectiveness data from PREVENT used in the economic analyses are from a TNF-alpha inhibitor naïve population only using a different composite response criterion to that used in clinical practice: o Are these data suitable to generate cost effectiveness estimates for an NHS population?
Technical team preliminary judgement and rationale	The composite response criteria may classify considerably more patients as responders, and consequently extend the use of the treatments to patients that do not respond as well. Given no evidence on the extent of response to these criteria was submitted, the impact on cost-effectiveness is unknown.

Issue 4– Pooling load and no-load dose data for secukinumab

Background/description of issue	PREVENT is a 3-armed parallel group study, in which secukinumab is given either with or without a loading dose compared with placebo. The 'loading' dose is administered subcutaneously at weeks 0,1,2,3 and 4 followed by monthly doses. During clarification, the company stated that the loading dose was recommended by the European Medicine Agency (EMA) for the treatment of rad-axSpA and that this was also the anticipated recommendation for the nr-axSpA marketing authorisation. The rationale for this decision was not clarified by the company. The trial arm with "no load"

dosing for secukinumab was primarily to satisfy FDA (US Food and Drug administration) criteria. The **company** therefore considered results for secukinumab with load dose only in its analyses.

The **ERG** did not think using evidence from the loading arm of PREVENT only was appropriate to establish the effectiveness of secukinumab as [redacted].

In response to clarification, the **company** argued that [redacted]. The **ERG** note that this [redacted].

ASAS 40, BASDAI50, change from baseline BASDAI and change from baseline BASFI for load and no-load arms of secukinumab. 16-weeks results from PREVENT trial

Outcome	Load secukinumab	No load secukinumab
ASAS40, n/N(%)	[redacted]	[redacted]
BASDAI50, n/N(%)	[redacted]	[redacted]
BASDAI change from baseline, mean (SD)	[redacted]	[redacted]
BASFI change from baseline, mean (SD)	[redacted]	[redacted]

Source: Table 12, ERG report (page 55)

An NMA on pooled load and no- load dose data carried out by the **ERG** showed that [redacted].

Why this issue is important	[redacted] The **ERG** notes that [redacted]
Questions for engagement	a. Would higher efficacy be expected for secukinumab with a loading dose in clinical practice? b. Given the similarity in clinical outcomes between the load and no-load dose arms at 16 weeks in PREVENT, can any differences in efficacy be expected beyond 16 weeks? c. Is pooling data for the load and no-load dosing regimens clinically appropriate and would the results be generalisable to clinical practice?
Technical team preliminary judgement and rationale	Due to the similarity in outcomes between the load and no-load arms, it is appropriate to pool the results to inform the effectiveness of secukinumab and reduce the uncertainty around the results.

Issue 5– Subgroup analyses of PREVENT according to MRI status and CRP status

Background/description of issue	Subgroup analyses were conducted by the **company** for those with evidence of inflammation from both MRI imaging and elevated CRP levels (MRI+/CRP+) compared to those with only one of the two (MRI-/CRP+ and MRI+/CRP-). The **ERG** noted that patients who have both types of objective signs of inflammation (i.e. CRP+ and MRI+) had better outcomes than the other two subgroups (CRP+/MRI- and CRP-/MRI+). The **ERG** considers that the [redacted]). The **company** highlighted that [redacted]

	[redacted] To understand the clinical effectiveness of secukinumab in patients who are CRP-/MRI-, the **ERG** requested the **company** to provide an indirect comparison of secukinumab with the available TNF-alpha inhibitor evidence in the CRP+/MRI+, CRP+/MRI-, CRP-/MRI+ subgroups. The company identified only one trial (of etanercept, called EMBARK) which had relevant, usable subgroup data and used Bucher's method to compare secukinumab with etanercept with placebo as the common comparator. Although the MRI-/CRP+ subgroup was very small (n=15), a [redacted] In response to clarification, the company also submitted cost effectiveness analyses according to MRI and CRP status. In the absence of randomised evidence on other comparators, this compared secukinumab with conventional care only and used data from the load and no-load arms in PREVENT. This suggests that secukinumab is more cost effective in the MRI+/CRP+ group compared with conventional care (Table 3, page 87 ERG report).
Why this issue is important	It is important to establish whether there are any groups of people for whom secukinumab would be more or less clinically and cost effective. Subgroup analyses from PREVENT suggests that [redacted] with both positive MRI imaging and elevated CRP levels (MRI+/CRP+). However, [redacted].
Questions for engagement	a. Would secukinumab be expected to be less effective in people who do not have elevated CRP levels or have a negative MRI scan in clinical practice? b. Are the results seen for the various subgroups generalisable to the subpopulations expected to be seen in clinical practice?Would secukinumab be considered for patients in the NHS who have a negative MRI scan? As most patients in the UK are diagnosed with non-radiographic axial spondyloarthritis based on a positive MRI, is this a clinically relevant subgroup?
Technical team preliminary judgement and rationale	[redacted]

Issue 6– Network meta-analyses

Background/description of issue	Secukinumab was compared to four TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab) in a network meta-analysis (NMA) as none of the active treatments were compared to each other directly in trials. The common placebo comparator was used to form a (star shaped) network connecting all the treatments and the outcomes included in the NMA were (i) ASAS40, (ii) BASDAI50, (iii) BASDAI change from baseline (CFB), and (iv) BASFI CFB as they would be used in the economic model. The **company's** base-case NMA included data from 7 RCTs at 16 weeks. A variety of NMA models were fitted, modelling outcomes independently and jointly, and making different assumptions about the data. The base case NMA incorporated in the economic modelling was based on the joint modelling approach used in TA383. In this model, responses on BASDAI50 and BASDAI change from baseline were related to each other and BASDAI and BASFI change from baselines were assumed to be correlated. All TNF-alpha inhibitors were assumed to have an exchangeable treatment effect, i.e. the treatment effects are similar but not identical. Inferences about the effectiveness of each TNF-alpha inhibitor borrow strength across the treatment class, shrinking the estimates towards the mean of the class effect. The **company** uses these shrunken estimates in their economic model. Only fixed effects-models were fitted, i.e. between-study heterogeneity was not considered in the joint modelling. Secukinumab generally showed [redacted]

	[redacted] As there are few trials included in the NMA and no-head-to-head comparisons of treatments, the **ERG** highlights that there is no potential for checking for consistency in the network, even though this is a fundamental assumption. The ERG carried out an analysis using alternative baseline values from EuroSpA instead of baseline parameters in PREVENT. [redacted].
Why this issue is important	The company considers that secukinumab efficacy may have been [redacted]. If there are meaningful differences in patient characteristics or trial conduct across the trials included in the NMA, these may lead to bias.
Questions for engagement	a. Are the results from the NMA clinically plausible? Is secukinumab expected to have poorer treatment effects compared to most TNF-alpha inhibitors? o Could the underestimation of the effect estimates for secukinumab in the NMA be attributed to the heterogeneity of trials in the NMA, higher baseline BASFI score, use of either load or non-load dose of secukinumab in trials, mixture of MRI/CRP positive sugbgroups in the trials (some of whom may benefit less)and lower % HLA-B27? b. Are the higher placebo response rates seen in PREVENT for ASAS40 and BASFI compared to trials for other TNF-alpha inhibitors likely to adversely affect the treatment effect estimates for secukinumab?
Technical team preliminary judgement and rationale	The NMA methods were appropriate and, although there is some heterogeneity between trials, this is unlikely to have substantially influenced the results. However, it is important to determine if secukinumab is expected to have poorer treatment effects compared to most TNF-alpha inhibitors in clinical practice and if the potential underestimation of the treatment effect estimates for secukinumab in the NMA can be explained.

Issue 7– Baseline BASDAI and BASFI scores conditional on response

Background/description of issue	Baseline BASDAI and BASFI scores represent the starting point for the model's cohort at the beginning of treatment. Baselines were assumed to be conditioned on response, i.e. responders to treatment are assumed to have a different baseline BASDAI and BASFI than non-responders to treatment. Baseline values conditional on response were only reported in 2 trials included in the NMA (PREVENT and in ABILITY-1). For a given baseline value for the overall population, the conditional baselines should also change as the proportion of responders changes. This means the conditional baselines will also change across NMA models. The **company** therefore derived conditional baseline scores using a relationship that required needing to further consider ratios between responder and non-responder baselines. Ratios were calculated for the 2 trials (PREVENT and the ABIITY-1). The **company** used the average ratio across secukinumab and adalimumab to derive the conditional baselines for the remaining TNF-alpha inhibitors. The appropriateness of the use of conditional baselines was considered in TA383 in which it was identified that the use of BASDAI50 as a response criterion means that individuals with higher BASDAI need to demonstrate a higher magnitude of absolute change in BASDAI to be classified as responders. This could mean that responders to BASDAI50 have a lower baseline BASDAI than non-responders. In TA383, the committee noted that this suggests that people with severe disease were less likely to have a clinically meaningful benefit than those with less severe disease. In clinical practice, the response criteria would be BASDAI50 or 2 units change in BASDAI, which the committee thought would obviate differences in the baselines. Therefore, the committee preferred the use of a common baseline across responders and non-responders. The **ERG** acknowledged that whether baselines should be conditional on response is an area of uncertainty. It noted that overall BASDAI and BASFI baselines are specified as a function of the probability of BASDAI50. Given that BASDAI50 varies with the NMA model, the baseline BASDAI and BASFI also vary. The ERG considered that baselines should be representative of the nr-axSpA population and should not depend on the chosen NMA model. The **ERG** also considered that the company's approach to derive the conditional baseline values (based on ratios) should reflect the observed data. The validity of the relationship determined by the ratios (that define conditional baseline values) when used to extrapolate across response rates and across treatments is unknown. Additionally, the **ERG** questions the appropriateness of using the average of the ratios of adalimumab and secukinumab to represent other TNF-alpha-inhibitors, particularly as baseline BASFI ratios are significantly

different (0.72 vs [redacted], respectively). The **ERG** considers the ratios for adalimumab may more appropriately reflect those expected of other TNF-alpha inhibitors.

The **ERG** notes that in the current appraisal the modelled response variable is BASDAI50 and, in line with the **company**, prefers to assume that baselines of BASDAI/BASFI differ across responders and non-responders to BASDAI50 (baselines conditioned on BASDAI50). However, the ERG corrects an error in the implementation of conditional baseline values in the company's approach and makes a further modification assuming the ratios for adalimumab more appropriately reflect those expected of other TNF-alpha inhibitors (rather than using the average ratio across secukinumab and adalimumab in the company's approach). The ERG highlighted that the assumption of conditional baselines is supported by trial evidence from PREVENT and ABILITY-1 as shown below:

	SEC (PREVENT)	ADA (ABILITY-1)	CC (PREVENT)	average ratio*
Baseline BASDAI values for responders	[redacted]	6.21	[redacted]	
Baseline BASDAI values for non - responders	[redacted]	6.53	[redacted]	
Ratio (responder vs. non-responder)	[redacted]	0.95	[redacted]	[redacted]
Baseline BASFI values for responders	[redacted]	3.6	[redacted]	[redacted]
Baseline BASFI values for non - responders	[redacted]	4.97	[redacted]	[redacted]
Ratio (responder vs. non-responder)	[redacted]	0.72	[redacted]	[redacted]
Change in BASDAI for responders	[redacted]	-4.79	[redacted]	[redacted]
Change in BASDAI for non-responders	[redacted]	-0.55	[redacted]	[redacted]
Ratio (responder vs. non-responder)	[redacted]	8.71	[redacted]	[redacted]
Change in BASFI for responders	[redacted]	-2.75	[redacted]	[redacted]
Change in BASFI for non-responders	[redacted]	-0.32	[redacted]	[redacted]
Ratio (responder vs. non-responder)	[redacted]	8.59	[redacted]	[redacted]

Source: Table 15(page 69 of ERG report) SEC:Secukinumab, ADA:Adalimumab, CC: Conventional care
*The average ratio is calculated from the SEC and ADA R/NR ratios and the CC ratio is not included

	The **company** provided a sensitivity analysis where common baseline BASDAI/BASFI scores were assumed across responders and non-responders. Changing to a common baseline model was also explored by the **ERG** in its own sensitivity analyses and favoured TNF-alpha inhibitors. The mechanism by which cost-effectiveness estimates change when the model changes to assume common baselines instead of conditional is complex and is reliant on the magnitude of the difference between the baseline values for responders and non-responders which is determined by the ratio.
Why this issue is important	The company's base case model assumes that baseline BASDAI and BASFI scores are conditional on response. The ERG's base case model also assumes conditional baselines but makes two changes (see above). Whether baselines should be conditional on response is an area of uncertainty and changing to a common baseline model significantly impacts cost-effectiveness estimates and favours TNF-alpha inhibitors. The ERG preferred to use conditional baselines because conditional baselines better reflect the available data and the use of the composite outcomes in clinical practice is now known to affect the proportion of responders significantly.
Questions for engagement	a. Should baseline BASDAI and BASFI values be conditioned on response? That is assuming responders to treatment have a different baseline BASDAI and BASFI than non-responders to treatment?
Technical team preliminary judgement and rationale	Although the committee in TA383 preferred the use of common baselines, the assumption of conditional baselines is supported by data available for BASDAI50 and should be the preferred approach. The technical team agrees with the modifications made by the ERG, that is, correcting an error in the implementation of conditional baseline values and assuming that the ratios for adalimumab reflect those expected of other TNF-alpha inhibitors.

Issue 8– Costs assumed for TNF-alpha inhibitors

Background/description of issue	To cost TNF-alpha inhibitors using a single comparator to reflect the class or when the model considered subsequent TNF-alpha treatment, the **company** used the 'market-share' information, averaged across months as below, although it did not specify the source of this market share data even when requested at clarification:

Biologic treatment	Jan'19	Feb'19	Mar'19	Apr'19	May'19	Jun'19	Jul'19	Aug'19	Sep'19	Oct'19

SEC	[redacted]											
CER P	[redacted]											
ETN	[redacted]											
ETN BS	[redacted]											
ADA	[redacted]											
ADA BS	[redacted]											
GOL	[redacted]											

SEC: Secukinumab, CER P: Certolizumab Pegol, ETN: Etanercept, ADA: Adalimumab, GOL: Golimumab, ETN BS: Etanercept Biosimilar, ADA BS: Adalimumab Biosimilar

The **ERG** considered that the **company's** market share data may not be representative of the expected use of TNF-alpha inhibitors in first line treatment in the UK. NICE currently recommends that, if more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen. A recently available (late 2018) biosimilar for adalimumab is the cheapest TNF-alpha-inhibitor in the market and its use in the NHS is expected to keep increasing. Therefore, the ERG believes that the costs of first-line TNF-alpha inhibitors are likely to be closer to the cost of adalimumab's biosimilar. In the base case analysis, it would therefore be reasonable to assume that for first-line use of seckinumab, the appropriate comparator would be the adalimumab's biosimilar. The company's approach of a mixed basket of TNF-alpha inhibitors is not likely to reflect the current levels of use of the cheapest alternative (adalimumab biosimilar).

The **company also** submitted evidence on second line use of secukinumab, based on the subgroup of TNF-experienced participants in the PREVENT trial. This subgroup is very small ([redacted]) and the **ERG** does not consider these analyses to be suitable for decision making. The **ERG** conducted exploratory analyses on the use of secukinumab second-line. These show that secukinumab is only cost-effective for second-line use if second-line TNF-alpha- inhibitors are costed using the company's market share data rather than biosimilars. However, note that underlying these analyses are a number of assumptions, such as the extent of reduction in effectiveness (at

	an equal level) for both secukinumab and TNF-alpha inhibitor, uncertainty over the BASFI and BASDAI scores at the start of second-line treatment and the fact that reason for discontinuation is not considered here. The ERG believes that second-line results for secukinumab should therefore be interpreted with caution.
Why this issue is important	The **ERG's** exploratory analyses of first-line secukinumab show that the costs used for TNF-alpha inhibitors are the key driver of cost effectiveness. The company's own results for first-line use indicate that secukinumab is slightly more costly and considerably less effective (dominated) than the adalimumab biosimilar, the cheapest TNF-alpha inhibitor available. Exploratory analyses of secukinumab second-line also show that secukinumab is only cost-effective if second-line TNF-alpha- inhibitors are costed using the company's market share data rather than biosimilars.
Questions for engagement	a. Which TNF-alpha inhibitor is most widely used in clinical practice? b. Is the use of the adalimumab biosimilar for first-line treatment likely to keep increasing as suggested by the ERG, to become the main TNF-alpha inhibitor used?
Technical team preliminary judgement and rationale	In line with TA383, the least expensive nationally available TNF-alpha inhibitor (taking into account administration costs and patient access schemes) should be used to represent the class for first-line treatment.

Issue 9– Subsequent treatments

Background/description of issue	In evaluating the cost-effectiveness of first-line use of secukinumab the **company's** base case model does not consider subsequent treatment with biologics. Given that patients are eligible (and likely) to receive further treatments, the **ERG** considered that it is important that the outcomes and costs of further lines of therapy are considered when establishing the cost-effectiveness of first-line use of secukinumab.. The **ERG** also considered whether conventional care should be the only comparator when secukinumab is given second-line. NICE recommends sequential use of TNFs (TA383) and hence these are relevant comparators to secukinumab in second-line treatment. The company argues against this by citing the Regional Medicines Optimisation Committee (RMOC) Advisory Statement on the use of biologics across conditions which recommends switching mechanism of action when a biologic treatment fails. However, the RMOC also highlights that if treatment failure can be attributed to the development of anti-drug antibodies, a second-line treatment of the same class may be preferable in order to avoid treatment interruption. The **ERG's** clinical advisor confirmed that this is a known mechanism for loss of response to TNF-alpha inhibitors in people with nr-axSpA.

	The **company** considered an exploratory scenario (a sequence model) in which all patients who did not respond to treatment during the induction period, or responded initially but subsequently discontinued maintenance therapy, received a 2nd-line biologic therapy. The **company's** base-case model assumes that discontinuation of 1st-line treatment is followed by a second induction period (of equal length to the first), at the end of which response was again assessed based on BASDAI50 and, conditional on response, patients entered a second Markov model (identical to the one used for first-line). The scenario analysis presented by the **company** compared secukinumab followed by a basket of TNF-alpha inhibitors with each TNF-alpha inhibitor followed by a basket of all other options. The **ERG** requested extensions to this model at clarification: • secukinumab followed by TNF-alpha-inhibitor • TNF-alpha-inhibitor followed by secukinumab • TNF-alpha-inhibitor followed by another TNF-alpha-inhibitor. In implementing these models, the **company** assumes the characteristics of the patients starting second-line treatment is based on the biologic-experienced subgroup in PREVENT ([redacted]). The BASDAI and BASFI values at the start of second-line are derived by weighting the treatment-specific first-line baseline values according to the proportion of use of each treatment as specified in the 'mixed-basket'. Also, the **company** assumes a reduction in effectiveness at second-line based on observed rates in PREVENT. Overall, BASDAI50 response was assumed to be reduced by [redacted], change from baseline BASDAI by [redacted], and BASFI change from baseline by [redacted]. The **ERG** notes that the **company's** model does not account for the fact that the baseline of patients that fail first-line treatment (and are hence eligible for second-line treatment) differs from those that respond to first-line treatment. Instead, all patients initiating second-line therapy (independently of whether they responded or not to first-line treatment) are assigned the same baselines only conditioned on their response in second-line. This means that the modelling of the patients' BASFI and BASDAI scores is incorrect in the sequence model submitted and the **company's model** can only be used when common baselines are considered. This means that the **company** model is restricted to the context of assuming common baselines and can only be used for decision-making in this context. Furthermore, the reduction in treatment effectiveness for subsequent treatments assumptions are based on the small subgroup of biologic-experienced patients in PREVENT which cannot be considered reliable. The **ERG**

	considers that evidence regarding the reduction in the effectiveness at second-line for TNF-alpha inhibitors based on registries in rad-axSpA such as the DANBIO registry is more suitable. This registry reports BASDAI50 response, median BASDAI, and median BASFI scores at baseline and at 3 months for first, second, and third line of treatment. Therefore, relative risks can be derived for reduction in BASDAI50 response, change from baseline BASDAI and change from baseline BASFI at second- and third-line, compared with first-line. In its base-case analysis, the ERG used the non-sequence model (which did not consider subsequent treatments) as the company's sequential model could only be used with common baselines. The ERG preferred to use the non-sequence model with conditional baselines because the direction of bias of not incorporating subsequent treatments is easier to predict.
Why this issue is important	Subsequent treatment costs may have a large impact on the ICER. It is important that the outcomes and costs of further lines of therapy reflecting clinical practice are considered when establishing the cost-effectiveness of secukinumab. In the **ERG's** sequence model explored in sensitivity analyses, subsequent treatments have a significant impact on cost-effectiveness estimates. The use of secukinumab in the first-line setting means the cheapest TNF inhibitor is reserved for second-line (adalimumab). When 2 TNF inhibitors are used, the first is costed at adalimumab's price but the second-is costed at etanercept's price. For both these reasons, sensitivity analyses exploring a treatment sequence model with common baselines show that considering subsequent treatments makes TNF inhibitors less favourable (but still cost-effective). The most significant reason for this difference being increased costs.
Questions for engagement	a. What subsequent treatments are patients likely to receive after first-line use of secukinumab in clinical practice? b. What are the relevant comparators for second-line secukinumab in clinical practice? Is a comparison of second- line use of secukinumab compared with other TNF-alpha inhibitors appropriate? c. Is the DANBIO registry a more suitable source for estimates of the reduction in effectiveness for subsequent treatments than the subgroup of biologic-experienced patients in PREVENT?
Technical team preliminary judgement and rationale	Subsequent treatment with biologics should be considered to establish the cost-effectiveness of first-line use of secukinumab. NICE recommends sequential use of TNFs (TA383) and hence these are relevant comparators when secukinumab is positioned as a second- line therapy. The **company's** treatment sequence model, informing the cost-effectiveness of second-line secukinumab, has been not been implemented correctly due to the limitations outlined above. Therefore, the ERG's analyses are preferred.

4. Issues for information

Tables 1 to 8 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Company's cost effectiveness results for first-line use of secukinumab using the combined load and no-load arms of secukinumab from PREVENT using conditional baselines

Treatment	Total costs	Total QALYs	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER (fully incremental)
CC	[redacted]	[redacted]	-	-	-
ADA biosimilar	[redacted]	[redacted]	£8,181	1.49	£5,491
SEC (pooled load/no load)	[redacted]	[redacted]	£8,265	1.06	Dominated
ETA biosimilar	[redacted]	[redacted]	£26,734	1.41	Dominated
CTZ	[redacted]	[redacted]	£30,521	1.64	£148,933
GOL	[redacted]	[redacted]	£33,023	1.65	£250,200

SEC: Secukinumab, CER P: Certolizumab Pegol, ETN: Etanercept, ADA: Adalimumab, GOL: Golimumab, CC: Conventional care
Source: Table 20 (page 84) of ERG report

Table 2: Company's cost effectiveness results for first-line use of secukinumab compared to a single TNF-alpha-inhibitor (combined load and no-load arms) using conditional baselines. Company's approach of a mixed basket of TNF-alpha inhibitors does not reflect the current levels of use of the cheapest alternative (adalimumab biosimilar).

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (fully incremental)
CC	[redacted]	[redacted]	-	-	-
SEC	[redacted]	[redacted]	[redacted]	£8,265	1.06

TNFi	[redacted]	[redacted]	[redacted]	£21,355	1.58

SEC: Secukinumab, CC: Conventional care, TNFi: TNF-alpha-inhibitor Source: Table 21 (page 85) of ERG report

Table 3: Company's sensitivity analysis for first-and second-line use of secukinumab assuming common BASDAI/BASFI baselines across responders and non-responders, a single TNF-alpha-inhibitor comparator and reduction in efficacy at second-line based on PREVENT data.

	Incremental costs vs. baseline	Incremental QALYs vs. baseline	ICER (fully incremental)
Sequencing model (reduced efficacy at second line for secukinumab and TNF-alpha-inhibitors)			
SEC-> TNFi	-	-	-
TNFi -> SEC	£4,342	0.39	£11,133
TNFi -> TNFi	£8,198	0.57	£21,422

SEC: Secukinumab, TNFi: TNF-alpha-inhibitor
Source: Table 22 (page 86) of ERG report

Table 4: Cumulative implementation of analyses leading to ERG's base case using the non-sequence model (i.e. not considering subsequent treatment with biologics) with conditional baselines (first-line use)

	Discounted costs			Discounted QALYs			ICER (first-line use of SEC) (TNFi->CC Vs SEC->CC)
	SEC -> CC	TNFi ->CC	CC	SEC -> CC	TNFi ->CC	CC	
Company's base-case (first-line use, load dosage)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,632 (for TNFi)
1. Company base-case, correcting model errors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,310 (for TNFi)

2. 1 + Costing TNFi based on ADA BS	[redacted]	[redacted]	[redacted]	£2,221 (for TNFi)
3. 2 + Baseline values based on EuroSpA[7] and change values for placebo based on pooling across relevant trials	[redacted]	[redacted]	[redacted]	£3,015 (for TNFi)
4. 3 + pooled secukinumab arms of PREVENT	[redacted]	[redacted]	[redacted]	£2,447 (for TNFi)
5. 4 + York utility algorithm **(ERG's base-case for first-line use)**	[redacted]	[redacted]	[redacted]	£1,673 (for TNFi)

Source: Table 25 (page 95 of ERG report)

Table 5: Sensitivity analyses on ERG's base case (first-line use)

Analyses (1-4) in table 5 consider the use of SEC at first line. The analyses compare two main strategies: SEC at first line followed by conventional care CC (SEC->CC) vs. TNFi at first line followed by CC (TNFi->CC). The last column reports ICERs of the SEC sequence vs. TNF sequence. Consider the first line that reports the ICER for the ERG's base case: it shows that the SEC sequence (SEC-> CC) is less costly than the TNFi sequence [redacted] but is also less effective [redacted]). This means that the ICER of the SEC sequence vs. the TNFi sequence will return a positive value £1,673 per QALY) but this is in the southwest (SW) quadrant (i.e. incremental costs and outcomes are both negative). Once in the SW quadrant, ICERs cannot be interpreted in the usual way: in the SW quadrant, the technology is cost-effective if the ICER is above the threshold! So SEC is not considered cost-effective at usual threshold values. The TNFi sequence has higher costs and effects than the SEC sequence, and the ICER, which will have the same value of £1,673 per QALY will then have the usual interpretation, indicating that it is the TNFi sequence that is

cost-effective. To highlight this, there is a note in the table (alongside the ICER values) to indicate over which technology the ICER can be interpreted in the usual way.

Analysis	Discounted costs			Discounted QALYs			ICER (first-line use of SEC)
	SEC ->CC	TNFi ->CC	CC	SEC ->CC	TNFi ->CC	CC	ICER (**SEC**-> CC vs **TNFi**-> CC)
ERG's base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,673 (for TNFi)
1. Common BASDAI and BASFI baselines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TNFi dpminates
2. Using No-load costs for SEC (Depending on marketing authorisation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,700 (for TNFi)
3. No BASFI progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,286 (for TNFi)
4. Company's market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,811 (for TNFi)
	SEC ->TNFi ->CC	TNFi ->TNFi ->CC	CC	SEC ->TNFi ->CC	TNFi ->TNFi ->CC	CC	ICER (**TNFi**->TNFi->CC vs **SEC**->TNFi->CC)
5. Treatment sequence with common baselines. Note that second TNFi is costed as etanercept biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,102 (for TNFi sequence)

Source: Table 26 (page 96 of ERG report)

Analysis 5 considers SEC at first line, but it assumes that after SEC fails, TNFi follows before CC (i.e. SEC->TNFi->CC). This strategy is compared with a sequence of two TNFs that are followed by CC (i.e. TNFi->TNFi->CC). This analysis suggests that TNFi->TNFi->CC, with an ICER of 12,102 for TNFi sequence, is more effective and more costly than SEC->TNFi->CC, and is cost-effective according to usual threshold values.

Table 6: Base-case and sensitivity analyses for second-line use of secukinumab

Note: NICE recommends sequential use of TNFs (TA383) and the ERG considered these to be relevant comparators to secukinumab in second-line treatment.

In table 6 SEC is considered only in second line. Specifically, two main strategies are compared: i) and a sequence of two TNFis followed by CC (TNFi->TNFi->CC) and ii) TNFi at first line followed by SEC at second line and then CC (TNFi->SEC->CC). The ICER of £43,312 can be interpreted in the usual way for TNFi->TNFi-> CC vs. TNFi->SEC->CC – the value of the ICER indicates that TNFi->TNFi->CC is not cost-effective at the usual 20-30k threshold values used by NICE.

Analysis	Discounted costs			Discounted QALYs			ICER (second-line use of SEC)
	TNFi ->TNFi ->CC	TNFi ->SEC ->CC	CC	TNFi ->TNFi ->CC	TNFi -> SEC ->CC	CC	ICER (**TNFi->SEC**-> CC vs **TNFi->TNFi**-> CC)
1. **ERG's base-case for second-line use of SEC (**costing second TNFi as ETA BS). Reduction in effectiveness based on DANBIO registry. Overall baseline based on non-responders to TNFi baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,312 (for TNFi sequence)
2. Different BASFI baseline values							

2a. Lower overall BASFI baseline (i.e. 5.948 - 1)	[redacted]	[redacted]	[redacted]	£43,362 (for TNFi sequence)
2b. Higher overall BASFI baseline (i.e. 5.948 + 1)	[redacted]	[redacted]	[redacted]	£43,799 (for TNFi sequence)
3. Common baselines	[redacted]	[redacted]	[redacted]	£42,466 (for TNFi sequence)
4. Costing second-line TNFi based on:				
4a. the most expensive TNFi (i.e. GOL)	[redacted]	[redacted]	[redacted]	£50,508 (for TNFi sequence)
4b. on company's market share	[redacted]	[redacted]	[redacted]	£26,509 (for TNFi sequence)
4c. ADA BS	[redacted]	[redacted]	[redacted]	TNFi dominates
5. Reduction in effectiveness is based on PREVENT evidence	[redacted]	[redacted]	[redacted]	£41,883 (for TNFi sequence)

Source: Table 27 (page 97 of ERG report)

Table 7: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Inadequate evidence for second-line use of secukinumab from PREVENT	The company's analyses of biologic-experienced patients is based on a very small subgroup from PREVENT (only [redacted] of the [redacted] patients recruited were biologic-experienced with only [redacted] being randomised to secukinumab with loading and [redacted] to placebo). Therefore, **Error! Reference source not found.**	Unknown
Clinical effectiveness of secukinumab compared TNF-alpha inhibitors	Although the ERG considered the NMA methodology to be appropriate and results from the NMA are included in the economic model, there is considerable uncertainty about the effectiveness of secukinumab compared to TNF-alpha inhibitors for nr-axSpA patients.	Unknown

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	Secukinumab shows similar efficacy to TNF-alpha inhibitors in rad-axSpA and the **ERG's** clinical advisor highlighted that rad-axSpA and nr-axSpA are perceived as parts of a spectrum of axSpA conditions. Hence, evidence of effect in rad-axSpA may have some relevance to a nr-axSpA population. However [redacted] when compared to secukinumab trials in rad-axSpA. The **ERG** therefore considers that, based on the current limited evidence, the NMA results should be considered at face-value.	
Use of conditional baseline BASDAI and BASFI	It remains uncertain whether baseline BASDAI and BASFI should be conditioned on response. The impact of this on cost-effectiveness in a model where subsequent treatments are considered is also unknown. Whilst conditional baselines have been justified on the basis of the use of the relative BASDAI50 criteria, the **ERG** believes that the composite response criteria used in clinical practice is likely to diminish such an effect.	Unknown
BASFI progression in the company model	The approach to modelling long-term BASDAI and BASFI in the **company** model was the same as in TA383. The assessment group in TA383 had originally intended to model long-term BASFI changes based on the rate of conversion from nr-axSpA to rad-axSpA. This implies that patients who do not develop radiographic symptoms maintain a constant BASFI, whilst patients who develop radiographic symptoms showing objective signs of inflammation on scans, and hence progress to rad-axSpA, are subject to the BASFI progression rate for rad-axSpA. However, due to the lack of evidence, the more simplified assumption was considered in TA383 such that all patients were assumed to incur progression in BASFI, albeit at a lower rate relative to the population with rad-an. In the current appraisal, and in	Overestimation of BASFI progression in the economic model

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	response to clarification questions, the **company** identified 3 recently published studies that informed the rate of progression from nr-axSpA to AS. The **ERG** also identified a recent study that systematically reviewed evidence of conversion to AS. Briefly, this study suggests that, based on the response criteria recommended by NICE, around 1% of nr-axSpA patients progress to AS every year suggesting a lower progression in BASFI than used in TA383. The **company**, however, did not use this information to extend the long-term BASFI model which means that the long-term BASFI progression may be overestimated in the company's model.	
Uncertainty over the treatment effect modification of long-term progression	The committee for TA383 considered it to be biologically plausible for physical function (measured by BASFI) to continue deteriorating during TNFa-inhibitor treatment despite the limited evidence but at a slower rate compared with the natural history of the disease. They also supported the assumption that treatment effects are sustained through the duration of treatment, despite the assessment group testing alternative assumptions. In the current appraisal, the **company** assumes the effect of secukinumab on BASFI progression to be equal to that of TNF-alpha-inhibitors. The **ERG** noted that PREVENT offered no evidence of such an effect for secukinumab. Therefore, there is uncertainty over the treatment effect modification of long-term progression.	Unknown

Table 8: Other issues for information

Issue	Comments
Patient selection and recruitment issues in PREVENT	PREVENT included a 'randomised set' for analysis which indicated that some patients may have been 'mis-randomised' by being 'mistakenly randomised prior to the study site confirming all eligibility criteria had been met'. Mis-randomised patients who did not receive

Issue	Comments
	any study medication were excluded from the data analysis sets (and treated as screening failures), so results for the true 'intention-to-treat' dataset were not reported. However, patients who did receive study medication were included. No data was presented by the company to indicate how many ineligible patients were randomised and received treatment. However, the submitted interim clinical study report (CSR) reported that [redacted] The **ERG** also notes that for the full analysis set, 'where patients were assigned to the wrong CRP/MRI stratification group at the study site, stratification group was overwritten by actual stratum'. No data were presented on how often this occurred. Therefore, there are concerns about the generalisability of the PREVENT population due to the number of ineligible patients included across the numerous small study sites, and the accuracy of the recording and stratification of CRP/MRI status.
Open label escape treatment in PREVENT	Open label 'escape treatment' of 150mg secukinumab was available for all non-responders at 20 weeks. 'Response' was based on "the clinical judgement of disease activity by the investigator and the patient to reflect the real-world setting". Therefore, no response criteria were pre-specified for the escape. Nobody will have received a double dose. Our understanding from the CSR is that early escape could, in principle, occur regardless of randomised treatment group, so some patients who originally received SEC might be 'escaping' to exactly the same treatment at the same dose. The originally randomised treatment assignment remained blinded. Those who escaped to another biologic had to have a 12 week wash-out period before receiving it. The **ERG** had concerns about how relevant these criteria might be to the NHS setting which has implications for interpretation of the longer-term efficacy data. The company did clarify that the original randomised treatment assignment (secukinumab 150 mg or placebo) remained blinded for at least 20 weeks.e
Nr-axSpA population is clinically heterogeneous in clinical practice	The population in PREVENT mainly matches the eligible population in England and Wales. although the **ERG** notes that the nr-axSpA population in clinical practice is intrinsically a

Issue	Comments
	clinically heterogeneous one. Heterogeneity is further increased by methodological heterogeneity across trials in the NMA and across the NHS regarding interpretation of 'objective signs of inflammation', particularly with respect to 'elevated CRP'.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

Authors

Jane Adam

Appraisal committee chair

Sana Khan

Technical lead

Zoe Charles

Technical adviser

Janet Robertson

Associate director

With input from the lead team:

Brian Shine

Lead team member

Khalida Ismail

Lead team member

Pam Rees

Lead team member

NICE National Institute for Health and Care Excellence

Technical engagement response form

Secukinumab for treating non-radiographic axial spondyloarthritis [ID1419]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **Friday 29 January 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisery committees.

About you

Your name	**Natalie Bennett**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novartis Pharmaceuticals UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

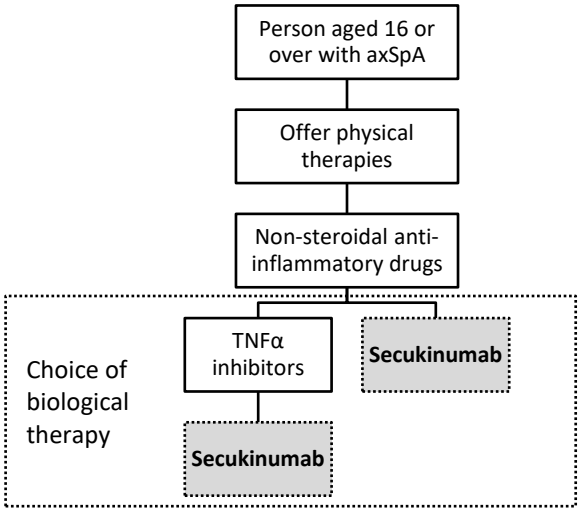
Questions for engagement

Issue 1: Place of secukinumab in the treatment pathway	
Is the proportion of patients in PREVENT treated with secukinumab who have previously had a TNF-alpha inhibitor (10%) reflective of the population in the NHS that would receive secukinumab?	In PREVENT, 21 patients (11%) of those treated with the secukinumab load regimen had failed previously on one biologic [1]. While it is likely that a higher proportion of patients will have received another biologic before receiving secukinumab in clinical practice, for some patients it would be appropriate to receive secukinumab first-line, particularly those who are contraindicated to tumour necrosis factor α (TNFα) inhibitors, such as those with multiple sclerosis (MS) and risk/history of tuberculosis (TB) infection. Data on second-line efficacy for other NICE-recommended treatments is also limited; trials for certolizumab pegol in non-radiographic axial spondyloarthritis (nr-axSpA) recruited similar proportions of patients with prior TNFα inhibitor exposure [2, 3], and golimumab, the most recently recommended option for nr-axSpA (expected to be used mainly in patients who have previously tried another biologic), was recommended based on evidence from the GO-AHEAD trial, which excluded patients with prior use of TNFα inhibitors [4]. PREVENT was the first nr-axSpA trial to report outcomes for the TNF inadequate response (TNF-IR) subgroup separately [1]. Our clinical adviser, Dr Raj Sengupta, explained that the inclusion of 10% of patients with previous use of biologic therapy is a good number to see in a trial and is more than some other biologic trials have recruited.
• Where is secukinumab most likely to be used in the treatment pathway? • Would secukinumab be used as a first-line biologic for treating nr-axSpA in clinical practice? • Would secukinumab be a treatment option for people when TNF-alpha inhibitors have proven to be ineffective or are not tolerated?	**Secukinumab should be available alongside current NICE-recommended biologics in first- and second-line to allow the right choice to be made depending on patient need.** It is anticipated that secukinumab will be used within its licensed indication, for treating active nr-axSpA with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs) [5]. We consider that secukinumab should be available both as an alternative first-line option for patients who have an inadequate response to NSAIDs or are contra-indicated to TNFα inhibitors, and as a second-line treatment option for patients who do not respond to TNFα inhibitors (Figure

- Would secukinumab be considered an alternative treatment option to TNF-alpha inhibitors in a first-line setting or is it more likely to be considered an option after treatment with TNF-alpha inhibitors has failed or is contraindicated?
- Is there a clinical need for secukinumab based on current clinical practice? What target population is likely to benefit most from treatment with secukinumab?

1). This would give clinicians the opportunity to choose the right treatment for specific patients, leading to improved adherence in the long-term [6-8]. As per the recommendation in TA383, it is expected that if more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) will be chosen [9].

Figure 1: NICE guideline for managing spondyloarthritis (including proposed positioning of secukinumab)



Abbreviations: axSpA, axial spondyloarthritis; TNFα, tumour necrosis factor alpha.

There is a clinical need for secukinumab in both first- and second-line.

Currently only TNFα inhibitors are recommended by NICE for treating nr-axSpA [9]. Secukinumab is the first interleukin-17A (IL-17A) inhibitor to be licensed for nr-axSpA, thereby offering an alternative mechanism of action.

Our clinical adviser explained that there are several reasons why first-line treatment with secukinumab may be the right choice for a patient, for example those with MS, TB, or a personal or family history of psoriasis. Other reasons include its safety profile (in randomised controlled trials [RCTs] and the real-world setting secukinumab had consistently demonstrated a safety

	profile with very low infection and cancer risk [5]), and administration frequency (monthly administration of secukinumab may be preferential for patients who travel frequently). The availability of an additional second-line treatment option would also be important for those who do not respond to TNFα inhibitor therapy. More than 45% of patients with nr-axSpA treated currently with TNFα inhibitors are not responding to treatment [10], and UK clinical expert advice suggests switching to a biologic with a new mechanism of action following primary failure may more effective than switching within class [11]. Novartis understands from clinical expert insights that in reality clinicians in England do not distinguish between ankylosing spondylitis (AS) and nr-axSpA; secukinumab is already approved by NICE for use as first-line biologic in the treatment of patients with AS [12]. In TA407 the clinical experts stated that the novel mechanism of action of secukinumab, and its other marketing authorisations for psoriasis and psoriatic arthritis, would give patients and clinicians a greater choice of targeted treatment options. We consider that some patients are likely to benefit most from first-line secukinumab, including those with TB, MS, a personal or family history of psoriasis, and those who are more likely to adhere to a therapy with monthly administration (rather than a more frequent regimen with other biologics). A patient expert stated that it is particularly important to have the option of a treatment with a different mechanism of action for patients whose disease did not respond to TNFα inhibitors. Secukinumab should be available both as an alternative first-line option for patients who have an inadequate response to NSAIDs or are contra-indicated to TNFα inhibitors, and as a second-line treatment option for patients who do not respond to TNFα inhibitors. This would give clinicians the opportunity to choose the right treatment based on individual patient needs. As per the recommendation in TA383, it is expected that clinicians will prescribe responsibly given the guidance wording to use the least expensive option if more than one treatment is suitable [9].
Are the trial results from the first-line setting generalisable to second-line use?	Relative effect estimates versus placebo were similar across the TNF-naïve and the TNF-experienced subgroups in PREVENT. [redacted] [redacted]

	[redacted] However, PREVENT was not powered to detect differences in the small subgroup of 54 patients with previous exposure to a TNFα inhibitor. In addition, PREVENT was the first nr-axSpA trial to report results for the TNF-IR subgroup separately [1]. We believe that secukinumab should be recommended in line with other biologics, which are available as options regardless of position in the treatment pathway, despite having limited data in the TNF-IR population [9].
Issue 2: High baseline BASFI in PREVENT trial population	
Is a population with an overall mean BASFI value of 6 representative of the those seen in the NHS?	Overall the cohort of patients in PREVENT is generalisable and representative of patients in the UK, although the mean baseline BASFI score (6.020) was higher than might be expected in clinical practice. However, mean values for BADSAI/BASFI scores were skewed by outliers.
Is the higher overall mean baseline BASFI value of 6 in PREVENT likely to adversely affect the trial and NMA results for secukinumab?	As lower BASFI is a predictor of response, effect estimates for secukinumab from PREVENT can be considered conservative. Although the evidence for a lower BASFI score being indicative of a good response relates to patients with AS, our clinical adviser confirmed that this also makes sense clinically for patients with nr-axSpA.
Are baseline BASFI values from the EuroSpA registry more representative of clinical practice in the UK?	Novartis would agree that baseline BASFI values from the EuroSpA registry are likely to be more representative of clinical practice in the UK, however combining baseline data from EuroSpa with change from baseline data from the trials is not ideal. We would like to note that there is no nr-axSpA-specific BASFI value in EuroSpA as the data do not distinguish between patients with AS and nr-axSpA.
Issue 3: Continuation of treatment criteria in PREVENT and longer-term clinical effectiveness	
Most patients in the trial continued treatment with secukinumab after 16 weeks. How does this impact interpretation of trial results given that continuation of treatment with secukinumab in clinical practice might be assessed on a different definition of 'response'?	The primary endpoint for all axSpA trials is ASAS20/40, as this is a regulatory requirement from the EMA and FDA. Secondary endpoints in PREVENT included BASDAI50 and change in BASDAI at Week 16, which are more reflective of the response criteria used in clinical practice [13]. It is important to note that the misalignment between trial and clinical practice response criteria also affects comparator therapies in nr-axSpA, so it is not clear what proportion of patients in PREVENT or other trials for NICE-recommended nr-axSpA therapies would fulfil the response criteria used in the NHS.

	We agree with the comment made by the technical team in the ongoing appraisal ID1532 Technical Report "The method used in the model (only using BASDAI data) to categorise patients as responders or non-responders to treatment does not reflect clinical guidelines, but the same approach has also been used in previously published models that were developed to assess the relative cost-effectiveness of treatments for axSpA (TA3831 and TA4072)." It is important that the committee is consistent across both these appraisals and with historical precedents.
Will the use of a different composite response criteria in clinical practice to that used in the PREVENT trial result in more patients as being classed as 'non-responders'?	The composite "OR" BASDAI 2-unit drop would result in more patients being classed as responders (not 'non-responders' as the question states). However, including the "AND" 2-unit spinal pain VAS drop would reduce the proportion of responders again, so the net directional effect is unclear. As discussed above, it is important to note that this issue applies not only to secukinumab but to all comparator treatments.
The long-term clinical effectiveness data from PREVENT used in the economic analyses are from a TNF-alpha inhibitor naïve population only using a different composite response criterion to that used in clinical practice: • Are these data suitable to generate cost effectiveness estimates for an NHS population?	Long-term treatment effect estimates in the economic analyses are based on Week 16 responder data extrapolated using assumptions of constant BASDAI and slowly increasing BASFI. Longer-term data from PREVENT are not inputs to the CE model; this approach is in line with TA383. The use of BASDAI50 and ASAS40 response criteria generates similar cost-effectiveness results. There are no comparator data using the composite response criteria used in clinical practice, so we were not able to explore the impact of that on cost-effectiveness results. Given the above, it is not clear what the directional effect on cost-effectiveness would be. Please note that the secondary analysis presents cost-effectiveness results for the biologic-experienced population (although not in comparison with TNFα inhibitors due to lack of comparator data).
Issue 4: Pooling load and no-load dose data for secukinumab	
Would higher efficacy be expected for secukinumab with a loading dose in clinical practice?	Yes. In PREVENT there was evidence of a faster onset of action as early as Weeks 2–3 with the loading regimen, and a consistent trend towards numerically higher efficacy responses with the loading regimen within the first 16 weeks. This was likely due to the inclusion of three additional loading doses and the observed differences in pharmacokinetics.

	These differences were not statistically significant, but statistical comparison of the load and no-load regimens was not pre-specified; the trial was designed to compare each of the arms with placebo.
Given the similarity in clinical outcomes between the load and no-load dose arms at 16 weeks in PREVENT, can any differences in efficacy be expected beyond 16 weeks?	The study was not powered to compare the load vs no-load regimens, but Week 52 results were broadly similar between the load and no-load regimens.
Is pooling data for the load and no-load dosing regimens clinically appropriate and would the results be generalisable to clinical practice?	Secukinumab load and no-load are considered separate interventions, and pooling of the two is not aligned with the EMA regulatory label [5]; the load regimen is the only licensed posology in the UK and is therefore the only regimen generalisable to UK clinical practice. It should be noted that in any analyses performed using the no-load dosing regimen it would be necessary to apply no-load costs in addition to efficacy data. The committee should be consistent in its approach to data from unlicensed treatment regimens across ID1419 and ID1532; in ID1532 the company only used data from licensed doses in their NMA, even though no statistically significant differences between the two loading doses studied was observed.
Issue 5: Subgroup analyses of PREVENT according to MRI status and CRP status	
Would secukinumab be expected to be less effective in people who do not have elevated CRP levels or have a negative MRI scan in clinical practice?	In PREVENT, all patients with objective signs of inflammation (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) derived benefit from treatment with secukinumab, with no differences in safety between subgroups. Novartis agrees with the ERG's conclusion that it is not possible to conclude on the heterogeneity of effect across CRP/MRI defined subgroups, as the trial was not powered to detect differences between these subgroups. Whilst it is possible that efficacy may be reduced in patients without elevated CRP or negative MRI, evidence in AS suggests that TNFα inhibitors may also be less effective in patients with lower CRP levels [14].
Are the results seen for the various subgroups generalisable to the subpopulations expected to be seen in clinical practice? Would secukinumab be	Secukinumab is indicated for treating active nr-axSpA with objective signs of inflammation as indicated by elevated CRP and/or MRI imaging evidence [5]. Therefore, secukinumab can be

considered for patients in the NHS who have a negative MRI scan? As most patients in the UK are diagnosed with non-radiographic axial spondyloarthritis based on a positive MRI, is this a clinically relevant subgroup?	prescribed to patients with a negative MRI scan providing they demonstrate elevated CRP and other symptoms suggesting inadequate management of the disease. Our clinical adviser confirmed that they would consider a patient with negative MR and elevated CRP to be suitable for secukinumab treatment, in line with NICE guidance for TNFα inhibitors [9].
Issue 6: Network meta-analyses	
Are the results from the NMA clinically plausible? Is secukinumab expected to have poorer treatment effects compared to most TNF-alpha inhibitors? • Could the underestimation of the effect estimates for secukinumab in the NMA be attributed to the heterogeneity of trials in the NMA, higher baseline BASFI score, use of either load or non-load dose of secukinumab in trials, mixture of MRI/CRP positive subgroups in the trials (some of whom may benefit less) and lower % HLA-B27?	Secukinumab is not expected to differ substantially from TNFα inhibitors. [redacted] The NMA findings represent the most robust estimate of relative treatment efficacy of secukinumab versus other biologics. However, given the limited evidence available, it is not possible to quantify the influence/impact of the identified factors (i.e. potential treatment-effect modifiers) upon the NMA results.
Are the higher placebo response rates seen in PREVENT for ASAS40 and BASFI compared to trials for other TNF-alpha inhibitors likely to adversely affect the treatment effect estimates for secukinumab?	Yes – differences in placebo response rates were a source of heterogeneity and could have adversely affected secukinumab treatment effect estimates. [redacted]

	In the PREVENT trial, higher placebo response rates were observed compared with previous older trials for the TNFα inhibitors (this phenomenon is not unique to PREVENT or secukinumab; for example, high placebo response rates were observed in the ixekizumab nr-axSpA trial [15]). Despite high placebo responses in PREVENT, all primary and secondary endpoints were met (at Week 16).
Issue 7: Baseline BASDAI and BASFI scores conditional on response	
Should baseline BASDAI and BASFI values be conditioned on response? That is assuming responders to treatment have a different baseline BASDAI and BASFI than non-responders to treatment?	The Novartis base case model assumes that baseline BASDAI and BASFI scores are conditional on response. We note that the ERG's base case model also assumes conditional baselines (with two changes). We agree with the ERG that the question on whether baselines should be conditional on response is an area of uncertainty, that conditional baselines better reflect the available data, and that the use of composite outcomes in clinical practice will affect the proportion of responders to some extent. However, this would also be the case for comparator treatments, not just secukinumab, and the ratio of changes from baseline for responders versus non-responders is uncertain for most anti-TNFs. The committee's preferences on this issue in TA383 were unclear.
Issue 8: Costs assumed for TNF-alpha inhibitors	
Which TNF-alpha inhibitor is most widely used in clinical practice?	The adalimumab biosimilar is the most widely used in clinical practice for nr-axSpA; data indicate that the adalimumab biosimilar has a [redacted] market share [16]. However, it is inappropriate to use the adalimumab biosimilar cost to represent the whole class of TNFα inhibitors given that: • adalimumab biosimilar does not represent the majority of prescriptions, • not all patients will receive adalimumab in first-line. For example, it is contraindicated in patients with moderate to severe heart failure, and prescribers should exercise caution in considering the use of adalimumab in pre-existing or recent-onset central or peripheral nervous system demyelinating disorders (e.g. MS). It would also be inappropriate to restrict access to secukinumab to second-line when it is substantially cheaper, and similarly effective, versus multiple other treatments that are recommended by NICE at first-line.
Is the use of the adalimumab biosimilar for first-line treatment likely to keep increasing as suggested by	Market share data indicate that adalimumab biosimilar usage is likely to keep increasing to become the main TNFα inhibitor used [16]. This view was supported by our clinical adviser,

the ERG, to become the main TNF-alpha inhibitor used?	however he emphasised that there will continue to be patients who are not suitable for first-line adalimumab, highlighting the importance of treatment choice (including secukinumab with its distinct mechanism of action) to provide patients with the most appropriate treatment options.
Issue 9: Subsequent treatments	
What subsequent treatments are patients likely to receive after first-line use of secukinumab in clinical practice?	Patients are likely to receive TNFα inhibitors, adalimumab, certolizumab pegol and etanercept after first-line use of secukinumab. This was supported by our clinical adviser. As per TA383, it is anticipated that the choice of treatment would be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available, and considering costs if more than one treatment is suitable [5].
What are the relevant comparators for second-line secukinumab in clinical practice? Is a comparison of second- line use of secukinumab compared with other TNF-alpha inhibitors appropriate?	We agree that TNFα inhibitors are relevant comparators for second-line use of secukinumab in clinical practice, a view supported by our clinical adviser. However, no randomised data on second or subsequent line use of TNFα inhibitors in nr-axSpA are available to inform cost-effectiveness estimates of second-line treatment options. In the Technical Report for ID1532, the technical team recognise that there is insufficient evidence to facilitate modelling of treatment sequencing and that this will therefore remain as an unresolvable uncertainty.
Is the DANBIO registry a more suitable source for estimates of the reduction in effectiveness for subsequent treatments than the subgroup of biologic-experienced patients in PREVENT?	No – we believe that although the number of TNF-IR patients in PREVENT was low, the availability of RCT data provides more robust evidence compared with evidence from the DANBIO registry, which did not have a control arm to inform relative efficacy. The DANBIO registry is also not based in the UK, so may not be generalisable to the UK population.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Secukinumab for treating non-radiographic axial spondyloarthritis [ID1419]

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Deadline for comments **Friday 29 January 2021**

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- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

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About you

Your name	**BSR Spondyloarthritis Special Interest Group**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Society for Rheumatology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

Issue 1: Place of secukinumab in the treatment pathway	
Is the proportion of patients in PREVENT treated with secukinumab who have previously had a TNF-alpha inhibitor ([redacted] reflective of the population in the NHS that would receive secukinumab?	**Around 20-30% of patients previously treated with TNF-alpha inhibitor may receive secukinumab**

Where is secukinumab most likely to be used in the treatment pathway? ○ Would secukinumab be used as a first-line biologic for treating nr-axSpA in clinical practice? ○ Would secukinumab be a treatment option for people when TNF-alpha inhibitors have proven to be ineffective or are not tolerated? ○ Would secukinumab be considered an alternative treatment option to TNF-alpha inhibitors in a first-line setting or is it more likely to be considered an option after treatment with TNF-alpha inhibitors has failed or is contraindicated? ○ Is there a clinical need for seckinumab based on current clinical practice? What target population is likely to benefit most from treatment with secukinumab?	**Yes** **Yes** **Both groups.** **Yes. Unmet need in nr-axSpA only as biologic treatment has been limited to TNF inhibitors thus far. Some patients do not tolerate or respond to NSAIDs and available biologic therapies**
Are the trial results from the first line setting generalisable to second line use?	**Yes.**
Issue 2: High baseline BASFI in PREVENT trial population	
Is a population with an overall mean BASFI value of 6 representative of the those seen in the NHS?	**Yes, in general**
Is the higher overall mean baseline BASFI value of 6 in PREVENT likely to adversely affect the trial and NMA results for secukinumab?	**No.**

Are baseline BASFI values from the EuroSpA registry more representative of clinical practice in the UK?	**Yes.**
Issue 3: Continuation of treatment criteria in PREVENT and longer-term clinical effectiveness	
Most patients in the trial continued treatment with secukinumab after 16 weeks. How does this impact interpretation of trial results given that continuation of treatment with secukinumab in clinical practice might be assessed on a different definition of 'response'?	**Long-term use and data beyond 16 weeks will be beneficial to assess the efficacy and persistence**
Will the use of a different composite response criteria in clinical practice to that used in the PREVENT trial result in more patients as being classed as 'non-responders'?	**These data are comparable**
The long-term clinical effectiveness data from PREVENT used in the economic analyses are from a TNF-alpha inhibitor naïve population only using a different composite response criterion to that used in clinical practice: • Are these data suitable to generate cost effectiveness estimates for an NHS population?	
Issue 4: Pooling load and no-load dose data for secukinumab	
Would higher efficacy be expected for secukinumab with a loading dose in clinical practice?	**Yes, from the data seen in radiographic axial spondyloarthritis this may be expected**
Given the similarity in clinical outcomes between the load and no-load dose arms at 16 weeks in PREVENT, can any differences in efficacy be expected beyond 16 weeks?	**A difference in efficacy in the two arms is not expected beyond 16 weeks**

Is pooling data for the load and no-load dosing regimens clinically appropriate and would the results be generalisable to clinical practice?	**This would seem appropriate within the study. The effect in clinical practice is to be determined.**
Issue 5: Subgroup analyses of PREVENT according to MRI status and CRP status	
Would secukinumab be expected to be less effective in people who do not have elevated CRP levels or have a negative MRI scan in clinical practice?	**This will be an area for further research and study**
Are the results seen for the various subgroups generalisable to the subpopulations expected to be seen in clinical practice?Would secukinumab be considered for patients in the NHS who have a negative MRI scan? As most patients in the UK are diagnosed with non-radiographic axial spondyloarthritis based on a positive MRI, is this a clinically relevant subgroup?	**This will be an area for further research and study**
Issue 6: Network meta-analyses	
Are the results from the NMA clinically plausible? Is secukinumab expected to have poorer treatment effects compared to most TNF-alpha inhibitors? ○ Could the underestimation of the effect estimates for secukinumab in the NMA be attributed to the heterogeneity of trials in the NMA, higher baseline BASFI score, use of either load or non-load dose of secukinumab in trials, mixture of MRI/CRP positive sugbgroups in the trials (some of whom may benefit less)and lower % HLA-B27?	**Yes. This will be an area for further research and study**

Are the higher placebo response rates seen in PREVENT for ASAS40 and BASFI compared to trials for other TNF-alpha inhibitors likely to adversely affect the treatment effect estimates for secukinumab?	**Yes. This will be an area for further research and study**
Issue 7: Baseline BASDAI and BASFI scores conditional on response	
Should baseline BASDAI and BASFI values be conditioned on response? That is assuming responders to treatment have a different baseline BASDAI and BASFI than non-responders to treatment?	**The BASDAI and BASFI values are based on cut-offs for disease activity**
Issue 8: Costs assumed for TNF-alpha inhibitors	
Which TNF-alpha inhibitor is most widely used in clinical practice?	**Adalimumab biosimilar and Etanercept biosimilar TNF-alpha inhibitors**
Is the use of the adalimumab biosimilar for first-line treatment likely to keep increasing as suggested by the ERG, to become the main TNF-alpha inhibitor used?	**Depending on the cost of other biosimilars available**
Issue 9: Subsequent treatments	
What subsequent treatments are patients likely to receive after first-line use of secukinumab in clinical practice?	**TNF-alpha inhibitors**
What are the relevant comparators for second-line secukinumab in clinical practice? Is a comparison of second- line use of secukinumab compared with other TNF-alpha inhibitors appropriate?	**Ixekizumab**

Is the DANBIO registry a more suitable source for estimates of the reduction in effectiveness for subsequent treatments than the subgroup of biologic-experienced patients in PREVENT?	

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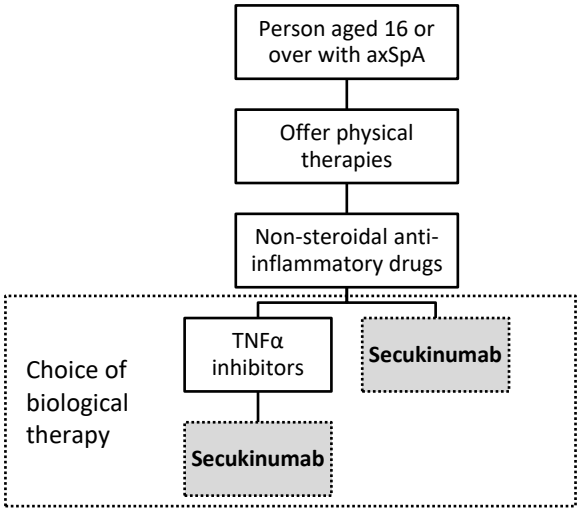
About you

Your name	**Natalie Bennett**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novartis Pharmaceuticals UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Questions for engagement		
Issue 1: Place of secukinumab in the treatment pathway		**ERG response**
Is the proportion of patients in PREVENT treated with secukinumab who have previously had a TNF-alpha inhibitor (10%) reflective of the population in the NHS that would receive secukinumab?	In PREVENT, 21 patients (11%) of those treated with the secukinumab load regimen had failed previously on one biologic [1]. While it is likely that a higher proportion of patients will have received another biologic before receiving secukinumab in clinical practice, for some patients it would be appropriate to receive secukinumab first-line, particularly those who are contraindicated to tumour necrosis factor α (TNFα) inhibitors, such as those with multiple sclerosis (MS) and risk/history of tuberculosis (TB) infection. Data on second-line efficacy for other NICE-recommended treatments is also limited; trials for certolizumab pegol in non-radiographic axial spondyloarthritis (nr-axSpA) recruited similar proportions of patients with prior TNFα inhibitor exposure [2, 3], and golimumab, the most recently recommended option for nr-axSpA (expected to be used mainly in patients who have previously tried another biologic), was recommended based on evidence from the GO-AHEAD trial, which excluded patients with prior use of TNFα inhibitors [4]. PREVENT was the first nr-axSpA trial to report outcomes for the TNF inadequate response (TNF-IR) subgroup separately [1]. Our clinical adviser, Dr Raj Sengupta, explained that the inclusion of 10% of patients with previous use of biologic therapy is a good number to see in a trial and is more than some other biologic trials have recruited.	The ERG notes that the inclusion criteria of PREVENT trial might mean that the trial is not representative of the UK population. It is therefore uncertain whether the 10% of patients in PREVENT with previous exposure to a TNFα inhibitor is a sensible estimate for the proportion of such patients in the NHS. The ERG agrees that patients with contraindications to TNFα inhibitors would also be eligible for secukinumab. The company have not provided any evidence on what proportion of patients these might be.

• Where is secukinumab most likely to be used in the treatment pathway? • Would secukinumab be used as a first-line biologic for treating nr-axSpA in clinical practice? • Would secukinumab be a treatment option for people when TNF-alpha inhibitors have proven to be ineffective or are not tolerated? • Would secukinumab be considered an alternative treatment option to TNF-alpha inhibitors in a first-line setting or is it more likely to be considered an option after	**Secukinumab should be available alongside current NICE-recommended biologics in first- and second-line to allow the right choice to be made depending on patient need.** It is anticipated that secukinumab will be used within its licensed indication, for treating active nr-axSpA with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs) [5].	The ERG concluded in its report that: "Secukinumab generally showed smaller effect estimates when compared to placebo than the TNFα inhibitors (except etanercept) for all outcomes and across all variations of the NMA performed". Additionally, ERG's analyses identified that secukinumab may not represent a cost-effective use of resources when compared to TNFα inhibitor treatment. This would suggest that secukinumab may not be a suitable alternative to TNFα inhibitors. It may, however, prove valuable where TNFα inhibitors have been ineffective or are contraindicated. The ERG notes that heterogeneity across trials, uncertainty over the impact of placebo response rates in NMAs, the small sample size in TNFα inhibitor experienced patients and the lack of evidence on TNFα-contraindicated patients and at last line of treatment, limits the certainty of our conclusions. The ERG also notes that secukinumab may be less effective, or ineffective, in patients with MRI

treatment with TNF-alpha inhibitors has failed or is contraindicated? • Is there a clinical need for secukinumab based on current clinical practice? What target population is likely to benefit most from treatment with secukinumab?	We consider that secukinumab should be available both as an alternative first-line option for patients who have an inadequate response to NSAIDs or are contra-indicated to TNFα inhibitors, and as a second-line treatment option for patients who do not respond to TNFα inhibitors (Figure 1). This would give clinicians the opportunity to choose the right treatment for specific patients, leading to improved adherence in the long-term [6-8]. As per the recommendation in TA383, it is expected that if more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) will be chosen [9]. **Figure 1: NICE guideline for managing spondyloarthritis (including proposed positioning of secukinumab)**  Abbreviations: axSpA, axial spondyloarthritis; TNFα, tumour necrosis factor alpha.	evidence, but without elevated CRP, or patients with elevated CRP, but no MRI evidence (see ERG report Table 4). See also Issue 5 (subgroups) As stated above, the ERG concluded that secukinumab may be inferior to TNFα inhibitors, as effect estimates were smaller for secukinumab in the network meta-analyses (although differences were not always statistically significant).

	There is a clinical need for secukinumab in both first- and second-line. Currently only TNFα inhibitors are recommended by NICE for treating nr-axSpA [9]. Secukinumab is the first interleukin-17A (IL-17A) inhibitor to be licensed for nr-axSpA, thereby offering an alternative mechanism of action. Our clinical adviser explained that there are several reasons why first-line treatment with secukinumab may be the right choice for a patient, for example those with MS, TB, or a personal or family history of psoriasis. Other reasons include its safety profile (in randomised controlled trials [RCTs] and the real-world setting secukinumab had consistently demonstrated a safety profile with very low infection and cancer risk [5]), and administration frequency (monthly administration of secukinumab may be preferential for patients who travel frequently). The availability of an additional second-line treatment option would also be important for those who do not respond to TNFα inhibitor therapy. More than 45% of patients with nr-axSpA treated currently with TNFα inhibitors are not responding to treatment [10], and UK clinical expert advice suggests switching to a biologic with a new mechanism of action following primary failure may more effective than switching within class [11]. Novartis understands from clinical expert insights that in reality clinicians in England do not distinguish between ankylosing spondylitis (AS) and nr-axSpA; secukinumab is already approved by NICE for use as first-line biologic in the treatment of patients with AS [12]. In TA407 the clinical experts stated that the novel mechanism of action of secukinumab, and its other marketing authorisations for psoriasis and psoriatic arthritis, would give patients and clinicians a greater choice of targeted treatment options. We consider that some patients are likely to benefit most from first-line secukinumab, including those with TB, MS, a personal or family history of psoriasis, and those who are more likely to adhere to a therapy with monthly administration (rather than a more frequent regimen with other biologics).	(see ERG report Table 9 and Figure 4) See also issue 6 (NMA). [No further ERG comments on this issue]

	A patient expert stated that it is particularly important to have the option of a treatment with a different mechanism of action for patients whose disease did not respond to TNFα inhibitors. Secukinumab should be available both as an alternative first-line option for patients who have an inadequate response to NSAIDs or are contra-indicated to TNFα inhibitors, and as a second-line treatment option for patients who do not respond to TNFα inhibitors. This would give clinicians the opportunity to choose the right treatment based on individual patient needs. As per the recommendation in TA383, it is expected that clinicians will prescribe responsibly given the guidance wording to use the least expensive option if more than one treatment is suitable [9].	
Are the trial results from the first-line setting generalisable to second-line use?	Relative effect estimates versus placebo were similar across the TNF-naïve and the TNF-experienced subgroups in PREVENT. [redacted] [redacted] [redacted]. However, PREVENT was not powered to detect differences in the small subgroup of 54 patients with previous exposure to a TNFα inhibitor. In addition, PREVENT was the first nr-axSpA trial to report results for the TNF-IR subgroup separately [1]. We believe that secukinumab should be recommended in line with other biologics, which are available as options regardless of position in the treatment pathway, despite having limited data in the TNF-IR population [9].	The ERG notes that [redacted] [redacted] [redacted] but he subgroup of experienced participants was too small to provide any conclusive evidence about [redacted] [redacted] It is, however, plausible secukinumab to be equally effective in first or second line use. The ERG confirms the [redacted] in experienced patients, but this may be due to a [redacted] in biologically-experienced patients, than any

		[redacted]. It may also be a chance finding.
Issue 2: High baseline BASFI in PREVENT trial population		
Is a population with an overall mean BASFI value of 6 representative of the those seen in the NHS?	Overall the cohort of patients in PREVENT is generalisable and representative of patients in the UK, although the mean baseline BASFI score (6.020) was higher than might be expected in clinical practice. However, mean values for BADSAI/BASFI scores were skewed by outliers.	No ERG comment. [Requires clinical expertise]
Is the higher overall mean baseline BASFI value of 6 in PREVENT likely to adversely affect the trial and NMA results for secukinumab?	As lower BASFI is a predictor of response, effect estimates for secukinumab from PREVENT can be considered conservative. Although the evidence for a lower BASFI score being indicative of a good response relates to patients with AS, our clinical adviser confirmed that this also makes sense clinically for patients with nr-axSpA.	The ERG cannot rule out that the higher BASFI in PREVENT compared to other trials in the NMA may have led to a lower ranking for secukinumab. However, no analysis has been presented to investigate this, and it appears to be speculative. The ERG therefore considers that the NMA as presented is the most robust evidence to compare secukinumab with other agents.
Are baseline BASFI values from the EuroSpA registry more representative of clinical practice in the UK?	Novartis would agree that baseline BASFI values from the EuroSpA registry are likely to be more representative of clinical practice in the UK, however combining baseline data from EuroSpa with change from baseline data from the trials is not ideal. We would like to note that there is no nr-axSpA-specific BASFI value in EuroSpA as the data do not distinguish between patients with AS and nr-axSpA.	The ERG, in its base case analysis, sourced the baseline values for BASFI from 1,178 individuals with nr-axSpA who were biologic-naïve, as reported in the EuroSpA registry. All models used estimates of the relative effectiveness of treatments (BASDAI 50, change from baseline on BASFI and BASDAI) derived from the NMA.

		Combining a baseline value with a relative effectiveness estimate sourced from a different study assumes that the two estimates can reasonably be considered independent. This assumption is commonly made in the analysis and interpretation of RCTs, and also underlies many of the analyses conducted by the manufacturer, such as the NMA. The manufacturer has not presented any evidence that could challenge this assumption.
Issue 3: Continuation of treatment criteria in PREVENT and longer-term clinical effectiveness		
Most patients in the trial continued treatment with secukinumab after 16 weeks. How does this impact interpretation of trial results given that continuation of treatment with secukinumab in clinical practice might be assessed on a different definition of 'response'?	The primary endpoint for all axSpA trials is ASAS20/40, as this is a regulatory requirement from the EMA and FDA. Secondary endpoints in PREVENT included BASDAI50 and change in BASDAI at Week 16, which are more reflective of the response criteria used in clinical practice [13]. It is important to note that the misalignment between trial and clinical practice response criteria also affects comparator therapies in nr-axSpA, so it is not clear what proportion of patients in PREVENT or other trials for NICE-recommended nr-axSpA therapies would fulfil the response criteria used in the NHS. We agree with the comment made by the technical team in the ongoing appraisal ID1532 Technical Report "The method used in the model (only using BASDAI data) to categorise patients as responders or non-responders to treatment does not reflect clinical guidelines, but the same approach has also been used in previously published models that were developed to assess the relative cost-effectiveness of treatments for axSpA	The company acknowledges the misalignment between response criteria in trials and clinical practice. As highlighted in the ERG report, recent evidence from a UK cohort [reference 38] suggests that the composite response criteria may classify considerably more patients as responders. The company does not provide information from their trials on the proportion classed as responders to the composite criteria (used in clinical practice). The company correctly identifies that the models previously used for

	(TA3831 and TA4072)." It is important that the committee is consistent across both these appraisals and with historical precedents.	NICE's decision making for comparator therapies in nr-axSpA have also only evaluated cost-effectiveness models based on the BASDAI50 criteria. However, a key consideration in this appraisal is that the evidence suggests that secukinumab may be less effective than alternatives, and that it [redacted] [redacted]*. In this situation, by classifying considerably more patients as responders, the composite response criteria means extending the use of secukinumab in patients that do not respond as well. This implies that such a continuation rule would worsen the cost-effectiveness profile of secukinumab (the ratio of costs to QALYs would increase). This is also expected to happen to comparator treatments. Incrementally, we hypothesise that the ICER for this treatment under the composite clinical decision rule may increase, [redacted] in relation to TNFs. However, given the company has not provided evidence on the extent of response to clinical criteria (or on the outcomes of patients continuing
Will the use of a different composite response criteria in clinical practice to that used in the PREVENT trial result in more patients as being classed as 'non-responders'?	The composite "OR" BASDAI 2-unit drop would result in more patients being classed as responders (not 'non-responders' as the question states). However, including the "AND" 2-unit spinal pain VAS drop would reduce the proportion of responders again, so the net directional effect is unclear. As discussed above, it is important to note that this issue applies not only to secukinumab but to all comparator treatments.	
The long-term clinical effectiveness data from PREVENT used in the economic analyses are from a TNF-alpha inhibitor naïve population only using a different composite response criterion to that used in clinical practice: • Are these data suitable to generate cost effectiveness estimates for an NHS population?	Long-term treatment effect estimates in the economic analyses are based on Week 16 responder data extrapolated using assumptions of constant BASDAI and slowly increasing BASFI. Longer-term data from PREVENT are not inputs to the CE model; this approach is in line with TA383. The use of BASDAI50 and ASAS40 response criteria generates similar cost-effectiveness results. There are no comparator data using the composite response criteria used in clinical practice, so we were not able to explore the impact of that on cost-effectiveness results. Given the above, it is not clear what the directional effect on cost-effectiveness would be. Please note that the secondary analysis presents cost-effectiveness results for the biologic-experienced population (although not in comparison with TNFα inhibitors due to lack of comparator data).	

		treatment), the impact on cost-effectiveness is largely unknown.
Issue 4: Pooling load and no-load dose data for secukinumab		
Would higher efficacy be expected for secukinumab with a loading dose in clinical practice?	Yes. In PREVENT there was evidence of a faster onset of action as early as Weeks 2–3 with the loading regimen, and a consistent trend towards numerically higher efficacy responses with the loading regimen within the first 16 weeks. This was likely due to the inclusion of three additional loading doses and the observed differences in pharmacokinetics. These differences were not statistically significant, but statistical comparison of the load and no-load regimens was not pre-specified; the trial was designed to compare each of the arms with placebo.	The ERG agrees that the loading dose may have had a faster onset of action, but results across all outcomes were consistent between loading and non-loading arms at 16 weeks and onwards.
Given the similarity in clinical outcomes between the load and no-load dose arms at 16 weeks in PREVENT, can any differences in efficacy be expected beyond 16 weeks?	The study was not powered to compare the load vs no-load regimens, but Week 52 results were broadly similar between the load and no-load regimens.	This is correct. There was no evidence of any difference in effect at 16 weeks or beyond.
Is pooling data for the load and no-load dosing regimens clinically appropriate and would the results be generalisable to clinical practice?	Secukinumab load and no-load are considered separate interventions, and pooling of the two is not aligned with the EMA regulatory label [5]; the load regimen is the only licensed posology in the UK and is therefore the only regimen generalisable to UK clinical practice. It should be noted that in any analyses performed using the no-load dosing regimen it would be necessary to apply no-load costs in addition to efficacy data. The committee should be consistent in its approach to data from unlicensed treatment regimens across ID1419 and ID1532; in ID1532 the company only used data from licensed doses in their NMA, even though no	The non-load dose is not licenced and as a consequence the ERG has focussed its critique and analyses on the load dose regimen. The ERG considers that the 16-week results from the load and no-load arms of PREVENT could be reasonably pooled to inform the effectiveness of secukinumab at 16 weeks and beyond (either regimen).

	statistically significant differences between the two loading doses studied was observed.	Given the similarity in outcomes across the two arms, combining the information will not affect expected results, but it can significantly reduce the existing uncertainty surrounding the treatment effect of secukinumab in relation to TNFα inhibitors.
Issue 5: Subgroup analyses of PREVENT according to MRI status and CRP status		
Would secukinumab be expected to be less effective in people who do not have elevated CRP levels or have a negative MRI scan in clinical practice?	In PREVENT, all patients with objective signs of inflammation (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) derived benefit from treatment with secukinumab, with no differences in safety between subgroups. Novartis agrees with the ERG's conclusion that it is not possible to conclude on the heterogeneity of effect across CRP/MRI defined subgroups, as the trial was not powered to detect differences between these subgroups. Whilst it is possible that efficacy may be reduced in patients without elevated CRP or negative MRI, evidence in AS suggests that TNFα inhibitors may also be less effective in patients with lower CRP levels [14].	The ERG disagrees with this statement. The ERG considers that there is only robust evidence of a benefit of secukinumab in the MRI+/CRP+ subgroup. In MRI+/CRP- and MRI-/CRP+ subgroups secukinumab is not statistically superior to placebo (see ERG report Table 4). This misrepresents the view of the ERG. As the trial was not powered to detect differences between subgroups, this means only that we cannot be certain that any observed differences are genuine. The lack of power does not mean that differences can be ignored or assumed to be absent.

		There is currently insufficient evidence to tell whether lower effectiveness in MRI- or CRP- patients is specific to secukinumab, or a broader issue with all treatments.
Are the results seen for the various subgroups generalisable to the subpopulations expected to be seen in clinical practice? Would secukinumab be considered for patients in the NHS who have a negative MRI scan? As most patients in the UK are diagnosed with non-radiographic axial spondyloarthritis based on a positive MRI, is this a clinically relevant subgroup?	Secukinumab is indicated for treating active nr-axSpA with objective signs of inflammation as indicated by elevated CRP and/or MRI imaging evidence [5]. Therefore, secukinumab can be prescribed to patients with a negative MRI scan providing they demonstrate elevated CRP and other symptoms suggesting inadequate management of the disease. Our clinical adviser confirmed that they would consider a patient with negative MR and elevated CRP to be suitable for secukinumab treatment, in line with NICE guidance for TNFα inhibitors [9].	According to clinical advice given to the ERG, most patients in the UK diagnosed with nr-axSpA will have a positive MRI scan, but it is unclear how many patients might be considered for secukinumab in the MRI-/CRP+ group.
Issue 6: Network meta-analyses		
Are the results from the NMA clinically plausible? Is secukinumab expected to have poorer treatment effects	Secukinumab is not expected to differ substantially from TNFα inhibitors. [redacted]	This is not what the ERG concluded from the NMA. The ERG found that [redacted]

compared to most TNF-alpha inhibitors? • Could the underestimation of the effect estimates for secukinumab in the NMA be attributed to the heterogeneity of trials in the NMA, higher baseline BASFI score, use of either load or non-load dose of secukinumab in trials, mixture of MRI/CRP positive subgroups in the trials (some of whom may benefit less) and lower % HLA-B27?	[redacted] The NMA findings represent the most robust estimate of relative treatment efficacy of secukinumab versus other biologics. However, given the limited evidence available, it is not possible to quantify the influence/impact of the identified factors (i.e. potential treatment-effect modifiers) upon the NMA results.	[redacted] While these differences were not generally statistically significant, they were consistent across outcomes (which is unlikely to occur were there genuinely [redacted]. While heterogeneity in baseline parameters might explain these differences, it should not be presumed that they do. The ERG therefore considers that, based on the current limited evidence, the NMA results should be considered at face-value.
Are the higher placebo response rates seen in PREVENT for ASAS40 and BASFI compared to trials for other TNF-alpha inhibitors likely to adversely affect the	Yes – differences in placebo response rates were a source of heterogeneity and could have adversely affected secukinumab treatment effect estimates. [redacted]	The ERG disagrees with this position. While higher placebo response rates could impact the [redacted]

treatment effect estimates for secukinumab?	[redacted] In the PREVENT trial, higher placebo response rates were observed compared with previous older trials for the TNFα inhibitors (this phenomenon is not unique to PREVENT or secukinumab; for example, high placebo response rates were observed in the ixekizumab nr-axSpA trial [15]). Despite high placebo responses in PREVENT, all primary and secondary endpoints were met (at Week 16).	[redacted] there is no robust evidence to support this assertion [redacted] (as acknowledged in the company's response). Therefore, the ERG considers that the main NMA results (with lower effect estimates for secukinumab) should be considered the most robust analysis.
Issue 7: Baseline BASDAI and BASFI scores conditional on response		
Should baseline BASDAI and BASFI values be conditioned on response? That is assuming responders to treatment have a different baseline BASDAI and BASFI than non-responders to treatment?	The Novartis base case model assumes that baseline BASDAI and BASFI scores are conditional on response. We note that the ERG's base case model also assumes conditional baselines (with two changes). We agree with the ERG that the question on whether baselines should be conditional on response is an area of uncertainty, that conditional baselines better reflect the available data, and that the use of composite outcomes in clinical practice will affect the proportion of responders to some extent. However, this would also be the case for comparator treatments, not just secukinumab, and the ratio of changes from baseline for responders versus non-responders is uncertain for most anti-TNFs. The committee's preferences on this issue in TA383 were unclear.	The ERG discussed the use of conditional baselines in its report. We believe there is uncertainty as to whether baseline BASDAI and BASFI should be conditioned on response. On the one hand, conditional baselines may be justified on the basis of the use of the relative BASDAI 50 criteria. This assumption is supported by the evidence available from trials – Table 15 summarises evidence from PREVENT and ABILITY-1 and, in TA383, the ERG had access to data from other trials in AS and nr-AxSpA which also supported the assumption of conditional

		baselines. Given that the modelled response variable in the cost-effectiveness analysis is BASDAI50, the ERG's base-case, in agreement with the manufacturer's base case, has adopted the assumption of conditional baselines (baselines for BASDAI/BASFI differ across responders and non-responders to BASDAI50). On the other hand, the ERG believes the composite response criteria used in clinical practice is likely to diminish such an effect and obviate the differences in the baselines. This is in line with the committee's deliberations in TA383, as evidenced in the FAD, paragraph 6.41: "The Committee explored the uncertainties relating to key assumptions in the Assessment Group's cost-effectiveness analysis. The Committee discussed the first key stage of the model: the probability of initial response (defined as a 50% improvement in BASDAI score). The Committee heard that in the Assessment Group's model, 'responders' had lower baseline BASDAI and BASFI scores compared with 'non-

		responders' (a difference that was reduced in scenario 2). The Committee noted that this assumption implied that people with more severe disease did not benefit as much from TNF-alpha inhibitors as people with less severe disease, because someone with more severe disease (higher baseline scores) must have larger absolute improvements than someone with less severe disease to achieve a BASDAI 50 response. It concluded, based on discussion with clinical and patient experts, that there was no evidence to suggest that people with severe disease were less likely to have a clinically meaningful benefit than those with less severe disease." For this reason, the ERG conducted sensitivity analysis to assess the impact of the alternative assumption of a common baseline– this is model 7 in sensitivity analyses. The comparison of models 5 and 7 highlights that changing to a common baseline model significantly determines cost-effectiveness. Note that the mechanism by which cost-effectiveness changes is complex and it is highly reliant on the magnitude of the difference

		between the baseline values for responders and non-responders (determined by the ratio) – note that the differences between model 5 and 7 fall mostly on TNF inhibitors which are assumed to have lowest ratio values than secukinumab. These analyses highlight that this is an area of uncertainty with significant impact on cost-effectiveness, hence the ERG would recommend the committee to consider both assumptions in their decision making.
Issue 8: Costs assumed for TNF-alpha inhibitors		
Which TNF-alpha inhibitor is most widely used in clinical practice?	The adalimumab biosimilar is the most widely used in clinical practice for nr-axSpA; data indicate that the adalimumab biosimilar has a [redacted] market share [16]. However, it is inappropriate to use the adalimumab biosimilar cost to represent the whole class of TNFα inhibitors given that: • adalimumab biosimilar does not represent the majority of prescriptions, • not all patients will receive adalimumab in first-line. For example, it is contraindicated in patients with moderate to severe heart failure, and prescribers should exercise caution in considering the use of adalimumab in pre-existing or recent-onset central or peripheral nervous system demyelinating disorders (e.g. MS). It would also be inappropriate to restrict access to secukinumab to second-line when it is substantially cheaper, and similarly effective, versus multiple other treatments that are recommended by NICE at first-line.	A biosimilar for adalimumab has been recently made available (late 2018) and is the cheapest TNFα-inhibitor in the market (see Table 16, ERG report). According to the company's data reproduced in Table 17, the market share of adalimumab biosimilar was 53% in October 2019 and is expected to increase. Hence, the ERG believes that adalimumab's biosimilar should be considered as the comparator for 1st line use of secukinumab.

Is the use of the adalimumab biosimilar for first-line treatment likely to keep increasing as suggested by the ERG, to become the main TNF-alpha inhibitor used?	Market share data indicate that adalimumab biosimilar usage is likely to keep increasing to become the main TNFα inhibitor used [16]. This view was supported by our clinical adviser, however he emphasised that there will continue to be patients who are not suitable for first-line adalimumab, highlighting the importance of treatment choice (including secukinumab with its distinct mechanism of action) to provide patients with the most appropriate treatment options.	The results of analyses highlight that in first line, secukinumab is [redacted] [redacted]) than adalimumab (biosimilar).This suggests that 1st line use of secukinumab does not represent a cost-effective use of resources. The evidence available on the effectiveness and cost-effectiveness of secukinumab at other lines of therapy is very limited. Exploratory analyses suggest that 2nd line use of secukinumab may be cost-effective in relation to 2nd line use of TNFα inhibitor – note that higher costs have been assumed for the 2nd line TNFα inhibitor under the assumption that the least expensive TNFα inhibitor, adalimumab's biosimilar, has already been used in 1st line. Due to the limitations in the evidence base, this conclusion should, however be tentative. No evidence has been presented by the company on the use of secukinumab in patients to which TNFα inhibitor treatment is contraindicated.

Issue 9: Subsequent treatments		
What subsequent treatments are patients likely to receive after first-line use of secukinumab in clinical practice?	Patients are likely to receive TNFα inhibitors, adalimumab, certolizumab pegol and etanercept after first-line use of secukinumab. This was supported by our clinical adviser. As per TA383, it is anticipated that the choice of treatment would be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available, and considering costs if more than one treatment is suitable [5].	The ERG notes two issues here. First: when considering only one line of treatment, there is no 'buffer' for a less effective 1st line choice (like secukinumab). So secukinumab's cost-effectiveness is likely to improve when subsequent treatments are considered (i.e. in the sequence model). Second: in the ERG's sequence model, the use of secukinumab in 1st line allows reserving the cheapest TNF inhibitor for 2nd line (adalimumab biosimilar). The comparator (two lines of TNF inhibitor treatment) considers the costs of adalimumab biosimilar at 1st line and of etanercept biosimilar at 2nd line. For both these reasons, model 7 vs model 12 (Table 26 of the ERGs report) highlights that considering subsequent treatments makes TNF inhibitors' cost effectiveness less favourable (but still cost-effective); the most significant reason for this difference is the increased costs of 2nd line TNF inhibitor treatment. Note that, as highlighted in our ERG report, the company's sequential

		model could only be used with common baselines.
What are the relevant comparators for second-line secukinumab in clinical practice? Is a comparison of second-line use of secukinumab compared with other TNF-alpha inhibitors appropriate?	We agree that TNFα inhibitors are relevant comparators for second-line use of secukinumab in clinical practice, a view supported by our clinical adviser. However, no randomised data on second or subsequent line use of TNFα inhibitors in nr-axSpA are available to inform cost-effectiveness estimates of second-line treatment options. In the Technical Report for ID1532, the technical team recognise that there is insufficient evidence to facilitate modelling of treatment sequencing and that this will therefore remain as an unresolvable uncertainty.	We agree that the use of both TNFs and secukinumab at 2nd line (and subsequent lines) should be considered uncertain, as the evidence of effectiveness is not robust.
Is the DANBIO registry a more suitable source for estimates of the reduction in effectiveness for subsequent treatments than the subgroup of biologic-experienced patients in PREVENT?	No – we believe that although the number of TNF-IR patients in PREVENT was low, the availability of RCT data provides more robust evidence compared with evidence from the DANBIO registry, which did not have a control arm to inform relative efficacy. The DANBIO registry is also not based in the UK, so may not be generalisable to the UK population.	The reduction in treatment effectiveness for subsequent treatments in the CS was informed by the biologic-experienced subgroup of PREVENT. However, the ERG notes that this subgroup is very small [redacted]) and hence estimates derived from it cannot be considered reliable. The estimates from the DANBIO registry [reference 51 in the ERG's report] relate to reductions in effectiveness for 2nd and 3rd line treatment in relation to 1st line treatment using relative risks. In the absence of more reliable evidence, we consider these estimates to be relevant to inform the current appraisal.

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